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14. ABSTRACT

Impaired autonomic-cardiac regulation, as defined by reduced levels of heart rate variability (HRV), is an independent predictor of death in patients with coronary artery disease (CAD) and a history of myocardial infarction. Moreover, transient shifts in HRV have been observed before the acute onset of ambulatory myocardial ischemia in CAD patients. The present study investigated whether or not changes in autonomic-cardiac regulation: (1) were associated with altered hemodynamic regulation in CAD patients; (2) could identify CAD patients at-risk for ambulatory myocardial ischemia; or (3) were related to changes in physical exertion and heart rate levels before the onset of ambulatory myocardial ischemia. Fifty-three patients with documented CAD (44 men; mean age 65 years) participated in 48-hours of ambulatory electrocardiographic (Holter), physical activity, and blood pressure monitoring. Holter tapes were analyzed for evidence of myocardial ischemia and were used to generate several indices of HRV, including markers for sympathetic and parasympathetic tone, and their ratio, sympathovagal tone. Results indicated that CAD patients with lower levels of HRV ($n = 26$) had significantly higher levels of heart rate than did patients with preserved levels of HRV ($n = 27$; $p < .05$), whereas HRV was found to be unrelated to patients blood pressure levels ($ps > .05$). Contrary to predictions, ischemic CAD patients ($n = 9$) were found to have significantly higher levels of HRV and significantly lower levels of heart rate when compared to non-ischemic patients ($n = 44$; $ps < .05$). These differences were not related to patients medication regimens, ejection fraction, or history of reperfusion procedures ($ps > .05$). Ischemic and non-ischemic CAD patients did not differ in terms of their HRV, heart rate, or blood pressure levels during prescribed non-ischemic periods of matched low and high physical activity ($ps > .05$). Regarding ambulatory ischemia (18 episodes), results indicated that there was a steady, significant increase in physical activity ($p < .05$) and heart rate levels ($p < .05$) over the half-hour preceding the onset of ischemia. During the peak in this activity (i.e., for the 10 minutes preceding ischemia), there was also a corresponding increase in sympathovagal balance ($p < .05$). The duration of ischemia was significantly longer in CAD patients with lower levels of 24-hour vagal tone ($p < .05$). Collectively, these findings suggest that activity-related changes in autonomic tone and heart rate are complicit in the induction of exertional ischemia. In conclusion, the findings of this study revealed that global markers of HRV do not discriminate CAD patients at-risk for ischemia, but are nonetheless important variables to consider whenever investigating the triggering of ambulatory myocardial ischemia by periods of heightened physical activity and cardiac demand levels. Study limitations include the low incidence of ambulatory ischemia a possible consequence of keeping patients on their medications during their participation in this study. Future research should consider analyzing HRV in a larger sample of CAD patients at risk for myocardial ischemia.

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ABSTRACT

Title of Dissertation: Autonomic and Hemodynamic Correlates of Daily Life Activity and Ambulatory Myocardial Ischemia in Patients with Stable Coronary Artery Disease

John F. Quigley, Doctor of Philosophy, 2003

Dissertation directed by: David S. Krantz, Ph.D.,
Professor and Chair, Department of Medical and Clinical Psychology

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= 27; $p < .05$), whereas HRV was found to be unrelated to patients' blood pressure levels (p 's $> .05$). Contrary to predictions, ischemic CAD patients ($n = 9$) were found to have significantly higher levels of HRV and significantly lower levels of heart rate when compared to non-ischemic patients ($n = 44$; p 's $< .05$). These differences were not related to patients' medication regimens, ejection fraction, or history of reperfusion procedures (p 's $> .05$). Ischemic and non-ischemic CAD patients did not differ in terms of their HRV, heart rate, or blood pressure levels during prescribed non-ischemic periods of matched "low" and "high" physical activity (p 's $> .05$). Regarding ambulatory ischemia (18 episodes), results indicated that there was a steady, significant increase in physical activity ($p < .05$) and heart rate levels ($p < .05$) over the half-hour preceding the onset of ischemia. During the peak in this activity (i.e., for the 10 minutes preceding ischemia), there was also a corresponding increase in sympathovagal balance ($p < .05$). The duration of ischemia was significantly longer in CAD patients with lower levels of 24-hour vagal tone ($p < .05$). Collectively, these findings suggest that activity-related changes in autonomic tone and heart rate are complicit in the induction of exertional ischemia.

In conclusion, the findings of this study revealed that global markers of HRV do not discriminate CAD patients at-risk for ischemia, but are nonetheless important variables to consider whenever investigating the "triggering" of ambulatory myocardial ischemia by periods of heightened physical activity and cardiac demand levels. Study limitations include the low incidence of ambulatory ischemia – a possible consequence of keeping patients on their medications during their participation in this study. Future research should consider analyzing HRV in a larger sample of CAD patients at risk for myocardial ischemia.

Autonomic and Hemodynamic Correlates of Daily Life Activity
and Ambulatory Myocardial Ischemia in Patients
with Stable Coronary Artery Disease

by

John F. Quigley

Dissertation submitted to the Faculty of the Department of Medical and Clinical
Psychology Graduate Program of the Uniformed Services University
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Dedication

This dissertation is dedicated to my family (past, present, and future) out of my respect and admiration for all of the accomplishments you have achieved – both as individuals and as professionals. The collective examples you have set for me have not gone unnoticed and, in part, are responsible for my motivation to complete this manuscript. Throughout my life you have had faith in me, shown me respect and compassion, treated me honestly, and loved me unconditionally. Your examples of personal courage and honor in the face of adversity as well as your lightheartedness and affability in day-to-day life have inspired me to want to become more like you. I am proud to consider myself your husband, brother, father, in-law, uncle, nephew, and most of all son, and I am truly blessed for having had the honor of sharing my life with you. You are the laugh behind my smile, the courage behind my strength, and the love within my heart. Simply put, you are all my personal heroes. Thank you for being you, so that I could learn how to become me. I love you, John.

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TABLE OF CONTENTS

INTRODUCTION	1
Background Information	3
Pathophysiology and Acute Manifestation of Coronary Artery Disease	3
Relationship Between Activity-Related Hemodynamic and Autonomic Stress Responses and the Onset of Myocardial Ischemia	3
Difficulties in Predicting Who Will Experience Daily Life Ischemia	5
Compromised Autonomic-Cardiac Regulation as a Predictor of Daily Life Ischemia	6
Physical and Mental Activity as Triggers of Myocardial Ischemia	7
Coronary Artery Disease, Endothelial Dysfunction, and Disturbances in the Supply of and Demand for Oxygenated Blood by the Heart	7
Physical Activity-Induced Increases in Cardiac Demand as a Trigger of Daily Life Ischemia	9
Physical Activity, Cardiac Demand, and the Circadian Onset of Daily Life Ischemia	12
Physical Activity, Coronary Blood Supply, and the Circadian Onset of Daily Life Ischemia	15
Mental Stress and the Onset of Myocardial Ischemia	17
Laboratory Investigations of Mental Stress Ischemia	17
Mental Stress and the Onset of Daily Life Ischemia	21
Differences Between CAD Patients With and Without Activity-Related Ischemia	23
Rationale for Investigating Autonomic-Cardiac Regulation in CAD Patients..	24
Measuring and Interpreting Heart Rate Variability	25
An Overview of Autonomic-Cardiac Regulation	25
Heart Rate Variability	27
Methods for Analyzing Heart Rate Variability	28
Time Domain Analyses	29
Frequency Domain Analyses	31
Low Frequency Power	31
High Frequency Power	32
Sympathovagal Tone	32
Special Considerations Affecting HRV Estimates	33
Alterations in Heart Rate Variability with Coronary Artery Disease	35
Myocardial Infarction and Reduced Heart Rate Variability.....	36
Uncomplicated CAD and Reduced Heart Rate Variability.....	37
Contrary Findings.....	40
Changes in HRV with Myocardial Ischemia.....	41

Alterations in Heart Rate Variability During Activities and Activity-Related Ischemia.....	43
The Effect of Physical Activity on Heart Rate Variability.....	43
Physical Activity, Changes in Heart Rate Variability, and the Onset of Daily Life Myocardial Ischemia.....	45
The Effect of Mental Activity on Heart Rate Variability.....	48
Mental Stress, Changes in Heart Rate Variability, and the Onset of Myocardial Ischemia.....	49
Summary and Rationale.....	51
Study Overview, Objectives, and Hypotheses.....	51
Study Overview.....	51
Study Objectives.....	52
HYPOTHESES.....	52
METHODS.....	53
Subjects.....	53
Procedure.....	54
Instrumentation.....	55
Structured Diary System.....	58
Power Analysis.....	59
Statistical Analysis.....	59
RESULTS.....	60
Patient Characteristics.....	61
Demographics.....	61
Clinical Status.....	61
Ambulatory ECG analyses	62
Ambulatory Physical Activity, Blood Pressure, and Heart Rate Monitoring.....	63
Physical Activity.....	63
Ambulatory Blood Pressure and Heart Rate.....	64
Structured Diary.....	64
Hypothesis 1: Reduced Heart Rate Variability as a Predictor of Higher 24-Hour Heart Rate and Blood Pressure Levels and Ischemic Burden.....	66
Hypothesis 2: Group Differences in Heart Rate Variability, Heart Rate, and Blood Pressure for Patients with and without ST-Segment Depression During Non-ischemic Periods of “Low” and “High” Physical Activity.....	69
Hypothesis 3: Changes in Physical Activity, Heart Rate, and Heart Rate Variability Prior to the Onset of Ambulatory Ischemia.....	71

DISCUSSION.....	74
Reduced Heart Rate Variability as Related to Differences in Hemodynamic Tone and Ischemic Burden.....	74
Differences in Autonomic and Hemodynamic Parameters Between CAD Patients with and without Evidence of Ambulatory Myocardial Ischemia.....	77
Comparing the Autonomic-Hemodynamic Stress Response of CAD Patients with and without Ischemia during Prescribed Periods of “Low and “High” Non-Ischemic Physical Exertion.....	80
Changes in Physical Activity, Heart Rate, and HRV before the Onset of Ambulatory Myocardial Ischemia.....	81
Study Limitations.....	84
Low Occurrence of Ambulatory Ischemia.....	84
24-hour HRV and the Risk for Ambulatory Ischemia.....	85
Ambulatory Blood Pressure Measurements.....	87
Difficulties in Identifying Non-Ischemic Control Groups.....	88
Future Research.....	88
Clinical Implications.....	90
Summary	91
APPENDICES.....	93
TABLES.....	96
FIGURES.....	105
REFERENCES.....	118

INTRODUCTION

Cardiovascular disease (CVD) is the leading cause of death in the United States, and is a pervasive health risk for millions of American adults. Nearly one-quarter of the population has diagnosed CVD (Center for Disease Control and Prevention, 2000), including 12,000,000 people with coronary artery disease (CAD; American Heart Association, 2003). CAD is characterized by the insidious and progressive narrowing of the coronary arteries by deposits of fibro-fatty cellular materials, otherwise known as atherosclerosis. In turn, CAD results in significant perfusion defects such as myocardial ischemia and myocardial infarction (MI), both of which result from an insufficient supply of oxygenated blood to the heart. In addition, CAD can also compromise autonomic-cardiac regulation by altering parasympathetic and sympathetic input to the heart and circulatory system. Altered cardiac neuroregulation is also related to the onset of MI and ischemia. Therefore, over the past two decades researchers have investigated how certain behaviors, including both physical and mental activities, can "trigger" acute coronary symptoms through their exacerbation of CAD sequelae. It is known that periods of heightened activity can augment the hemodynamic and autonomic stress responses of CAD patients, and may therefore lead to the onset of coronary events by exacerbating the oxygenation defects implicit to coronary disease. It remains unclear, however, as to why some CAD patients experience such events while others do not. Therefore, the relationship between physical and mental activities and the clinical manifestation of coronary disease warrants further investigation.

The purpose of this study is to examine how physical and mental activities lead to alterations in autonomic-cardiac regulation, cardiac workload, and the onset of daily life ischemia in patients with stable coronary artery disease. While aspects of this model have been previously tested (Quigley, 2000), the current study postulates that individual differences in underlying autonomic tone can differentiate CAD patients with and without evidence of daily life ischemia. Specifically, a currently untested hypothesis is that CAD-related disturbances in parasympathetic (i.e., vagal) input to the heart may influence the relationship between physical and mental activities and changes in heart rate (HR) and blood pressure (BP) related to the onset of ambulatory myocardial ischemia in CAD patients. Hypothetically, CAD patients with a reduced vagal capacity may be more likely to experience ischemia as a result of exaggerated HR and BP responses to activity-induced increases in sympathetic drive to the heart. Consequently, this study proposes to investigate both hemodynamic as well as autonomic correlates of daily life activity, and activity-related ischemia, in an attempt to identify both who and why certain CAD patients express acute manifestations of their disease.

Overview of Proposal. What follows is a brief review of background information that outlines several topics that are discussed in detail in this proposal. This review will be followed by a discussion on the role of physical and mental activity as triggers of myocardial ischemia. Subsequently, there will be a detailed review of autonomic-cardiac regulation, its measurement, its alteration by physical and mental activities, and its relation to the onset of myocardial ischemia. Finally, the hypotheses of the current study will be presented, as will the study methodology, results, and discussion sections.

Background Information.

Pathophysiology and Acute Manifestation of Coronary Artery Disease. Coronary artery disease can develop silently over many years, if not decades, via the development of atherosclerotic plaque formations in the inner lining of the coronary arteries. As CAD worsens, it is not uncommon for coronary blood flow to be obstructed by the atherosclerotic narrowing of the arterial lumen, or to be restricted inappropriately via abnormal coronary vasomotor activity related to the presence of CAD. Consequently, reduced myocardial oxygenation can ensue, provoking the onset of myocardial infarction or ischemia. By definition, an MI occurs when atherosclerotic coronary occlusion is complete, and portions of heart muscle die as a result of oxygen starvation. On the other hand, myocardial ischemia is a transient phenomenon and is oftentimes asymptomatic, occurring when there is an imbalance between the supply of and demand for oxygenated blood by the heart. In either case, the hemodynamic and autonomic correlates of elevated physical and mental activity are believed to exacerbate the perfusion defects caused by atherosclerosis, resulting in the precipitation of ischemic conditions.

Relationship Between Activity-Related Hemodynamic and Autonomic Stress Responses and the Onset of Myocardial Ischemia. In both healthy individuals as well as in patients with coronary disease, the hemodynamic stress response which results from strenuous activities (i.e., increased HR and BP) occurs, in part, as a result of a withdrawal in parasympathetic input to the heart, and at higher levels of exertion, an increase in sympathetic drive to the heart (Fagraeus & Linnarsson, 1976; Robinson, Epstein, Beiser, et al., 1966). That is, there appears to be a primary autonomic and secondary

hemodynamic stress response elicited by elevated activity levels. In CAD patients, however, such abrupt changes in myocardial oxygenation requirements may lead to the provocation of ischemia as a result of CAD-attenuation of oxygenated blood supply to the heart. In such instances, the hemodynamic demands associated with higher activity levels trigger the onset of ischemia by elaborating the perfusion defects implicit to coronary disease.

However, not every period of heightened activity, HR, or BP will result in the onset of ischemia in CAD patients, nor will every period of sedentary activity (i.e., \square HR, \square BP) remain ischemia-free. In other words, the hemodynamic correlates of activity do not exclusively predict the onset of ischemia in CAD patients. The question remains, however, as to whether or not changes in autonomic-cardiac regulation serve as a better predictor.

For example, several studies have shown that a withdrawal in vagal activity consistently precedes the onset of myocardial ischemia, and is oftentimes coupled with an increase in sympathetic drive to the heart (Brouwer, Portegies, Haaksma, et al., 1994; Goseki, Matsubara, Takahashi, et al., 1994; Vardas, Kochiadakis, Manios, et al., 1996; Vardas, Skolidis, Simandirakis, et al., 1994). This rearrangement of autonomic-cardiac regulation is quite similar to that induced by elevated activity levels, however few studies have investigated this coincidence, particularly with regard to the onset of ischemia. Moreover, while several studies have documented an immediate increase in HR and BP before the onset of ischemia (Deedwania & Nelson, 1990; Krantz, Kop, Gabbay, et al., 1996a; Parker, Testa, Jimenez, et al., 1994), other studies have observed a similar increase in cardiac demand before the onset of nocturnal ischemia, when patients were

asleep (Barry, Campbell, Yeung, et al., 1991). Because significant changes in activity do not occur during sleep, it is unlikely that these hemodynamic changes are activity-related. On the other hand, significant changes in HR and BP cannot occur independently of the autonomic nervous system (Guyton & Hall, 1996), suggesting that pre-ischemic increases in cardiac demand may be, in part, neurally mediated. Finally, and perhaps most importantly, is the fact that coronary disease is known to permanently alter cardiac vagal tone in some CAD patients (Task Force, 1996). Compromised vagal regulation may thereby serve as a primary risk factor for myocardial ischemia by predisposing such patients to exaggerated HR and BP responses to stress. Therefore, the autonomic and hemodynamic stress responses of CAD patients to periods of elevated exertion appear to be integral, interactive factors in the provocation of myocardial ischemia.

Difficulties in Predicting Who Will Experience Daily Life Ischemia. A final issue to consider is the difficulty in predicting who will or will not experience episodes of daily life ischemia. For instance, research has found that only about 30-40% of CAD patients with evidence of laboratory-based, exercise-induced ischemia will have episodes of daily life ischemia (Deanfield, Maseri, Selwyn, et al., 1983). By comparison, only about 50% of CAD patients with laboratory-induced mental stress ischemia will have episodes of daily life ischemia (Blumenthal, Jiang, Waugh, et al., 1995; Gottdiener, Krantz, Howell, et al., 1994). The disparity between these percentages is typically attributed to the fact that the hemodynamic requirements associated with daily life activities rarely match those elicited during contrived laboratory procedures - most CAD patients spend the majority of their daily lives engaged in non-strenuous, sedentary activities (Gabbay, Krantz, Kop, et al., 1996; Schang & Pepine, 1977). While true, this explanation is also

limited because it stresses the importance of increased cardiac demand as a trigger of daily life ischemia. In other words, this rationale cannot address why ischemia also occurs during rest, sleep, or during other periods of low exertion. Alternatively, as proposed by this study, because CAD-compromised autonomic-cardiac regulation is believed to be permanent, significant changes in cardiac demand may be sufficient but not necessary for CAD patients to experience myocardial ischemia, particularly in the case of low-exertion ischemia. This study posits that activity-related increases in cardiac demand serve as a secondary insult to a primarily autonomic predisposition for myocardial ischemia.

Compromised Autonomic-Cardiac Regulation as a Predictor of Daily Life Ischemia. The current study predicts that patients with daily life ischemia will be those individuals with more severely compromised cardiac vagal tone. It is known that in MI survivors, for example, permanent disturbances in vagal regulation can result from the denervation of the heart with the loss of viable muscle tissue - a condition found to be predictive of death in this population (Bigger, Fleiss, Rolnitzky, et al., 1993; Bigger, Fleiss, Rolnitzky, et al., 1991; Bigger, Fleiss, Steinman, et al., 1992; Bigger, Kleiger, Fleiss, et al., 1988; Kleiger, Miller, Bigger, et al., 1987; Wolf, Varigos, Hunt, et al., 1978). The question remains, however, as to whether or not similar deficiencies in vagal control predict who will or will not experience episodes of daily life ischemia, or whether these disturbances are exacerbated by varying degrees of physical and mental exertion. Thus, the current study was designed to address these issues, and begins by reviewing what is known about the relationship between physical and mental activities and the onset of daily life ischemia.

Physical and Mental Activity as Triggers of Myocardial Ischemia.

Coronary Artery Disease, Endothelial Dysfunction, and Disturbances in the Supply of and Demand for Oxygenated Blood by the Heart. Myocardial ischemia occurs in patients with coronary artery disease whenever the demand for oxygenated blood by the heart exceeds its supply. Therefore, in order to understand how periods of elevated activity can provoke ischemia, it is important to first consider how the development of atherosclerotic disease affects the functioning of the coronary arteries and their regulation of coronary blood flow.

For example, a key anatomical feature of the human arterial vasculature is the lining of the arterial walls by a protective mono-layer of endothelial cells. The primary function of this cell layer is to produce, release, and respond to numerous vasoactive substances in the bloodstream, with the purpose of regulating blood flow through the mediation of local vascular tone (Ralevic & Burnstock, 1993; Zeiher, Drexler, Wollschlaeger, et al., 1989). In the case of coronary blood flow, the response of the vascular smooth muscle to the release of endothelial-derived vasodilatory and constrictive substances is a respective increase or decrease in flow via the dilation or constriction of the vessel.

However, the development of CAD can injure the endothelium. In fact, a widely accepted explanation for the atherogenic process is the so-called "response-to-injury" hypothesis (Ross, 1993). The premise of this hypothesis is that endothelial lesions are a natural phenomenon resulting from the continuous exposure of the endothelium to blood turbulence (Ross, 1993). In turn, the body's natural healing process is to "scab" such

lesions via adherence and sub-endothelial migration of certain cellular materials. Under normal circumstances this process of cellular accumulation may dissipate once the integrity of the endothelium has been restored. However, when a particular area of the endothelium receives repeated injuries over an extended period of time, the accumulation of foamy, lipid laden, fibro-fatty cellular materials continues unabated, eventually resulting in the development of a sub-endothelial lesion. Under such circumstances, the endothelium is compromised by its separation from the underlying layer of vascular smooth muscle, its distension into and more pronounced exposure to blood flow turbulence, and in severe cases, its denudation and exposure of vascular smooth muscle to coronary blood flow.

In turn, activity-related ischemia is believed to occur when periods of elevated physical and mental exertion lead to a need for increased myocardial oxygenation - a need which cannot be satisfied due to the obstruction of coronary blood flow by atherosclerotic disease (Deedwania, 1997). Furthermore, these periods of activity can result in the release of vasoactive agents such as catecholamines into the bloodstream (Guyton et al., 1996). Exposure of vascular smooth muscle to catecholamines can result in vasoconstriction and a further restriction of oxygenated blood supply to the heart. Consequently, periods of elevated exertion exacerbate both the demand for, and the supply of oxygenated blood to the heart - a finding supported by angiographic studies of both exercise and mental stress-induced vasomotor activity (Gage, Hess, Murakami, et al., 1986; Yeung, Vekshtein, Krantz, et al., 1991). This same mechanism is believed to be responsible for the onset of daily life ischemia.

Physical Activity-Induced Increases in Cardiac Demand as a Trigger of Daily Life Ischemia. The increase in cardiac workload associated with physical activity is a potent trigger of myocardial ischemia. In fact, graded exercise stress test protocols are a standard by which vulnerability for ischemia is clinically diagnosed. In general, studies have found that CAD patients with evidence of exercise-induced laboratory ischemia are also more likely to experience episodes of daily life ischemia. Some of the first studies to examine this relationship were conducted by Deanfield and colleagues (Deanfield et al., 1983; Deanfield, Shea, Ribiero, et al., 1984b), who investigated the occurrence of daily life ischemia in CAD patients with exercise ischemia. Subsequently, the results of these initial studies underscore several important facts about daily life ischemia that are now widely accepted by the medical and scientific communities.

First, as mentioned earlier, only about 30-40% of CAD patients with laboratory-induced exercise ischemia usually experience episodes of daily life ischemia (Deanfield et al., 1983). While this percentage will vary from study to study, the relevant point is that the presence of daily life ischemia is not ubiquitous among CAD patients. This finding also leaves open the possibility that other phenomenological differences, such as comprised cardiac vagal regulation, may differentiate CAD patients with and without ambulatory ischemia. Second, Deanfield and colleagues found that most episodes of daily life ischemia occur at significantly lower HR levels than do episodes of exercise-induced ischemia. This difference in onset HR levels has since been explained by the fact that most people rarely engage in sustained, heightened physical activities during daily life that are comparable to those attained during structured exercise testing (Schang et al., 1977); standard exercise protocols typically entail rather brisk increments in workload

requirements (Panza, Quyyumi, Diodati, et al., 1991). Despite these differences in absolute activity levels, daily life ischemia is still most likely to occur during periods of moderate to intense physical activity (Gabbay et al., 1996). Third, Deanfield et al. (1984b) found that daily life ischemia usually occurs asymptotically, with less than 20% of daily life ischemic episodes being accompanied by angina. Exercise-induced ischemia, on the other hand, is commonly associated with anginal complaint, with Deanfield et al. (1983) reporting that 89% of their patients' exercise stress tests were accompanied by chest pain. Presumably, this disparity is due to the difference in physical exertion levels that are attained in laboratory settings versus daily life. Finally, despite the fact that daily life ischemia occurs at lower activity and onset HR levels than does exercise-induced ischemia, Deanfield (1983) as well as others (Barry et al., 1991; Deedwania et al., 1990; Krantz et al., 1996a; Parker et al., 1994), have found that significant increases in HR will oftentimes precede the onset of daily life ischemia, implicating increased cardiac demand as the trigger.

Subsequently, a number of daily life studies have found a link between heightened physical activity levels, increases in cardiac demand, and the occurrence of ambulatory ischemia. For example, a study by Quigley (2000) used automated physical activity monitors to continuously measure the activity levels of 21 CAD patients during daily life, and found that CAD patients had significantly higher levels of activity and HR during 54 episodes of myocardial ischemia than during non-ischemic times of the day. Consistent with previous findings, this study also found that a significant pre-ischemic increase in HR occurred in these patients, but in addition showed that this increase in cardiac demand was concomitant to a pre-ischemic increase in physical activity.

In a study by Krantz and associates (1996a), CAD patients' self-ratings of exertion were used to describe the relationship between daily life activities and the onset of ischemia. This study found that in 63 CAD patients, more than half (53%) of the 203 noted ischemic episodes occurred during periods of high activity and high heart rate. Such episodes also endured longer than did ischemic episodes occurring during periods of low physical activity.

For obvious reasons, nocturnal ischemia occurs at relatively lower levels of physical activity than does daytime ischemia. Still, the findings of Barry and colleagues (1991) highlight the fact that increases in activity during the night are related to the onset of myocardial ischemia. In this study, 21 stable CAD patients reported 36 episodes of nocturnal awaking and arising, of which 67% resulted in the onset of myocardial ischemia. Curiously, a pre-ischemic increase in HR also occurred in these patients, despite the fact that patients were still asleep when this increase in cardiac demand commenced. Therefore, besides the occurrence of nocturnal ischemia with changes in physical activity, Barry's findings also suggest that other factors, possibly neurogenic, are responsible for pre-ischemic increases in cardiac demand, considering that significant changes in physical activity are infrequent during sleep, and considering that significant changes in cardiac demand cannot occur without altered autonomic input to the heart and circulatory system (Guyton et al., 1996).

Finally, consistent with the studies cited above, Deedwania and Nelson (1990) showed that of the 92 episodes of daily life ischemia they observed in their study, 92% were preceded by a steady increase in cardiac demand. Specifically, 61% of these episodes were preceded by an increase in HR of 5 beats per minute (bpm) or more, while

73% of these episodes had an average increase in systolic blood pressure (SBP) of 10 or more millimeters of mercury (mm Hg). While this study did not assess patients' activity levels, these pre-ischemic increases in demand may still be activity-related, as was observed by Quigley (2000). On the other hand, Barry et al.'s (1991) observation of pre-ischemic HR increases during sleep again suggests that neural factors are also likely to be involved.

Physical Activity, Cardiac Demand, and the Circadian Onset of Daily Life Ischemia. Another important characteristic of daily life ischemia is the circadian distribution of its occurrence, and whether or not changes in daily life physical activity levels contribute to this pattern of onset. For example, previous daily life studies have characterized the circadian distribution of ischemia as having a peak incidence around morning awakening, with a lesser secondary peak in the late afternoon and early evening (Deedwania et al., 1990; Krantz et al., 1996a; Mulcahy, Keegan, Cunningham, et al., 1988; Parker et al., 1994; Pepine, 1991; Rocco, Barry, Campbell, et al., 1987). One of the first studies to examine this pattern was conducted by Rocco and colleagues (1987). These investigators showed that when the time of day at which CAD patients had ischemia was adjusted for the time of day at which each patient awoke (i.e., number of hours after awakening), a sharp increase in ischemic frequency was observed during the first three hours after morning arising. In other words, this study found that the onset of the peak in daily life ischemia began subsequent to the physical act of morning arising. In addition, Rocco et al. (1987) reported that 39% of all ischemic events and 46% of total ischemic time (i.e., total duration, in minutes) occurred in the morning hours, between 0600 and 1200 hours.

Subsequently, Parker and colleagues (1994) examined in more detail how the initiation of morning activities and changes in posture may be associated with the morning peak in daily life ischemia. After awaking subjects at the same time of day (8 a.m.), Parker delayed subjects' time of arising from bed by several hours in a counterbalanced fashion over two study days. As a result of this delayed arising, there was a similar observable delay in the onset of the peak in morning ischemia. In other words, by differentiating the time at which people awoke from the time at which people arose to begin their daily activities, the peak in morning ischemia appeared to be related to the act of arising. Furthermore, Parker reported that 87% of all the ischemic events observed in his study were preceded by HR increases of 5 bpm or more, implicating increases in cardiac demand as the mechanism by which ischemia was triggered. Moreover, on the days of delayed activity, Parker et al. (1994) observed that the peak incidence of HR-related ischemic events was likewise delayed, demonstrating the correspondence between activity-induced increases in cardiac demand and the onset of ischemia.

More recent correlational studies, such as that by Krantz and colleagues (1996a), have reported that 77% of morning ischemic episodes, and 51% of afternoon ischemic episodes occurred in patients self-reporting "high" activity levels during these times. "High activity" patients were almost four times more likely to experience morning ischemia, but also twice as likely to experience afternoon ischemia than patients reporting "low" activity levels. Self-reported activity levels were not related to an increased risk for evening ischemic episodes, however (Krantz et al., 1996a), suggesting that a different mechanism of action may be responsible for the provocation of ischemia during this time

of day. Finally, after controlling for patients' HR and self-reported physical and mental activities, Krantz et al. (1996a) found that a characteristic circadian distribution of ischemic events was maintained, with a morning peak at 0600 hours. The authors interpreted this finding as evidence of a possible endogenous triggering mechanism for myocardial ischemia.

As mentioned earlier, the onset of nocturnal ischemia has also been associated with increased physical activity levels, with periods of waking and arising during the night coinciding with the onset of ischemia 67% of the time (Barry et al., 1991). Increases in HR preceding nocturnal ischemia, as well as the frequency, duration, and recorded electrocardiogram (ECG) changes during ischemia were noted to be similar to those corresponding to ischemic events occurring with morning awaking. In other words, this study showed that changes in posture, such as arising from bed, can induce episodes of ischemia which are similar in nature, irrespective of the time of day at which they occur.

Finally, because the greatest risk for daily life ischemia is in the early morning hours, Quigley (2000) compared the objectively measured physical activity levels of CAD patients with and without evidence of ischemia upon morning awakening. The results of this study showed that, while pre-waking activity levels were similar between these groups of patients, CAD patients with ischemia upon awakening had a trend towards higher levels of physical activity subsequent to waking than did CAD patients without ischemia.

Collectively, these study findings demonstrate that the circadian onset of daily life ischemia appears to be related, in part, to periods of heightened physical activity and

cardiac demand. This finding appears to be true for the onset of ischemia with morning arising, as well as for ischemia occurring during periods of elevated activity in the afternoon and night. However, although these studies may neatly explain a cardiac demand-based model for activity-induced ischemia, one should also recognize that their findings cannot comment on the role of activity-induced changes in coronary blood supply, since there are no suitable ambulatory techniques currently available to measure supply. However, ample evidence from laboratory-based studies suggests that both physical activity and postural changes can diminish coronary blood supply levels via changes in coronary vascular tone (Brezinski, Tofler, Muller, et al., 1988; Gordon, Wolfe, Island, et al., 1966; Quyyumi, 1990; Weitzman, Fukushima, Nogeire, et al., 1971; Winther, Hillegrass, Tofler, et al., 1992), and may therefore also contribute to the circadian onset of daily life ischemia.

Physical Activity, Coronary Blood Supply, and the Circadian Onset of Daily Life Ischemia. There is evidence from angiographic investigations that stress-induced changes in coronary vascular tone can trigger the onset of myocardial ischemia by attenuating coronary blood supply levels (Gage et al., 1986; Yeung et al., 1991). Again, the proposed mechanism underlying this relationship is believed to be the exposure of the vascular smooth muscle layer to vasoactive substances released into the bloodstream during stress (i.e., catecholamines). As well, there is also evidence to suggest that the diurnal fluctuation of various humoral factors (including catecholamines), and their augmentation by changes in physical activity, may likewise contribute to the characteristic circadian onset of daily life ischemia, via alterations in coronary vascular

tone throughout the day (Brezinski et al., 1988; Gordon et al., 1966; Quyyumi, 1990; Weitzman et al., 1971; Winther et al., 1992).

For example, Gordon and colleagues (1966) observed that the early morning hours, as well as the postural changes related to morning arising, were associated with increased levels of renin, a powerful endogenous vasoconstrictor. Winther and associates (1992) reported that, regardless of the time of day, changing from a supine to an upright posture increased plasma norepinephrine levels an average of 50% above baseline levels. Increased plasma cortisol levels have also been found to occur with early morning physical activities and postural changes (Weitzman et al., 1971), and may act synergistically with heightened morning catecholamine levels (Turton & Deegan, 1974) to alter vasomotor tone. More recently, Quyyumi has reported that vascular tone appears to vary across the day due primarily to fluctuations in both systemic noradrenergic and renin activity (Quyyumi, Panza, Diodati, et al., 1992). Similarly, other factors involved in decreased coronary blood supply, such as increased sympathetic nerve activity (Fujita, Tanaka, Nakae, et al., 1998; Turton et al., 1974), increased platelet aggregability (Brezinski et al., 1988), and decreased fibrinolytic activity (Andreotti, Davies, Hackett, et al., 1988; Rosing, Brakman, Redwood, et al., 1970), are also known to vary across the day. Thus, it is likely that the diurnal ebb and flow of these humoral factors are augmented by, as well as overlap with, fluctuations in daily life physical activity levels. In turn, these findings suggest that heightened physical activity levels can exacerbate underlying physiological states related to diminished coronary blood supply which, in turn, probably act in concert with activity-induced increases in cardiac demand to trigger ambulatory ischemia.

Mental Stress and the Onset of Myocardial Ischemia. Evidence from both laboratory and daily life investigations highlight the fact that elevated levels of mental activity, particularly mental stress, are related to the onset of myocardial ischemia (Blumenthal et al., 1995; Burg, Jain, Soufer, et al., 1993; Dakak, Quyyumi, Eisenhofer, et al., 1995; Deanfield, Shea, Kensett, et al., 1984a; Goldberg, Becker, Bonsall, et al., 1996; Gottdiener et al., 1994; Gullette, Blumenthal, Babyak, et al., 1997; Kop, 1997; Kop, Gottdiener, Verdina, et al., 1995; Krantz, Kop, Santiago, et al., 1996b; La Veau, Rozanski, Krantz, et al., 1989; Rozanski, Bairey, Krantz, et al., 1988; Yeung et al., 1991). For example, laboratory investigations commonly report large BP and moderate HR increases with the onset of mental stress-induced ischemia, implicating increased cardiac demand as a trigger (Goldberg et al., 1996). However, these hemodynamic increases are usually much lower than those induced by exercise, although some studies have found similar increases in SBP with both types of stressors (Rozanski et al., 1988). Angiographic evidence suggests that mental stress-induced attenuation of coronary blood supply can also lead to the onset of ischemia (Yeung et al., 1991), similar to angiographic studies of exercise ischemia (Gage et al., 1986). Thus, similar to physical activity-induced ischemia, mental stress ischemia appears to result from the stress-induced imbalance between myocardial oxygen demand requirements and coronary blood supply levels.

Laboratory Investigations of Mental Stress Ischemia. With the use of adequate laboratory stressors, mental stress ischemia is inducible in 25-60% of CAD patients, depending upon the population under study (Goldberg et al., 1996; Rozanski et al., 1988; Rozanski, Blumenthal, & Kaplan, 1999). Commonly used mental stress tasks include

having patients perform arithmetic while being harassed by the research staff, or give a personally relevant public speech to staff, or recall an unresolved anger-provoking incident to staff, or to perform challenging standardized tasks such as the Stroop Word-Color test.

The recent Psychophysiological Investigations of Myocardial Ischemia or PIMI study, for example, used both a speech task as well as the Stroop Word-Color test to provoke laboratory ischemia in CAD patients (Goldberg et al., 1996). The purpose of this study was to investigate the role of stress-induced changes in hemodynamic and neurohormonal activity related to the onset of myocardial ischemia. In general, the findings of this comprehensive study showed that during mental stress, CAD patients had significant increases in HR, BP, and vascular resistance¹ over baseline values. While these changes in HR and BP were significantly lower than the respective changes observed during exercise, mental stress resulted in significantly higher levels of vascular resistance than exercise. Furthermore, epinephrine levels were similar between exercise and the mental stress speech task and were correlated with the changes in HR, SBP, rate-pressure product (RPP)² and total cardiac output (CO)³ during both mental stress tasks. Norepinephrine levels were also correlated with these hemodynamic parameters but only during the speech task. Finally, ischemic CAD patients were noted to have significant increases in vascular resistance, which did not occur in the non-ischemic patients, as well

¹ Vascular resistance refers to the amount of impedance blood flow incurs as it travels through a vessel. Resistance is inversely related to flow.

² Rate-pressure product is a gross measure of overall cardiac workload and is derived from the multiplication of concomitant HR and SBP.

³ Cardiac output is the total amount of blood disgorged by the heart per minute (L/min).

as greater increases in HR, BP, and RPP during mental stress. However, these groups did not differ with regard to circulating catecholamine levels, which were elevated in both groups during mental stress. Because the findings of the PIMI study highlight several important facts about the onset of mental stress ischemia, each will be discussed in detail.

First, the findings of PIMI reaffirm the fact that mental stress, similar to exercise, results in elevated levels of circulating catecholamines that correspond to heightened levels of cardiac workload in CAD patients. However, whereas exercise results in a normal decrease in systemic vascular resistance, with a correspondingly larger increase in CO, HR, BP, and RPP, mental stress results in increased resistance and more modest increases in workload. In other words, while both stressors elicit sympatho-adrenomedullary responses in CAD patients, mental stress may also lead to a reduction in coronary blood supply. Similar findings have also been reported by other researchers who have observed a transient decrease in EF⁴ with the onset of mental stress (Burg et al., 1993; La Veau et al., 1989).

Second, the increase in vascular resistance with mental stress was a distinguishing characteristic of ischemic CAD patients in PIMI, as were their significantly higher levels of HR, BP, and RPP during mental stress, compared to non-ischemic patients. Interestingly, CAD patients with and without ischemia did not differ significantly in workload parameters or resistance levels during exercise. Thus, the onset of mental stress ischemia appears to involve a more counterbalanced disruption of both cardiac demand

⁴ Ejection fraction is the amount of blood disgorged by the heart after systolic contraction and is considered to be an index of left ventricular function. Depressed EF values (i.e., <35%) indicates the possibility of left ventricular dysfunction.

and coronary blood supply levels than does exercise-induced ischemia, which is predominantly demand-based in origin.

Other laboratory studies have also reported mental stress-induced reductions in coronary blood supply in CAD patients as a result of increased vascular resistance. For example, Dakak and colleagues (Dakak et al., 1995) assessed the effects of a challenging video game on microcirculatory blood flow responses of 10 patients with minimal CAD and 5 healthy controls during cardiac catheterization. The results of this study showed that the coronary arteries of healthy subjects dilated modestly yet normally during mental stress (4%), and these subjects had a concomitant, significant, 26% decrease in coronary vascular resistance during the task. CAD patients, on the other hand, had an impaired vasodilatory response to mental stress, with some patients having a significant average vasoconstriction of 12% in their diseased arteries. Furthermore, all CAD patients had a non-significant average decrease in vascular resistance of only 9% during mental stress. This trend is consistent with angiographic findings of mental stress induced vasomotor activity (Yeung et al., 1991). Finally, Dakak et al. (1995) found that HR and BP responses as well as norepinephrine levels were similar between these two groups during mental stress, indicating that both CAD patients and healthy subjects attained similar levels of sympathetic arousal and cardiac workload during mental stress. Thus, the findings of Dakak et al. (1995) provide evidence that mental stress-induced changes in coronary blood supply related to resistance vessel activity, in combination with modest increases in cardiac workload, are likely to be operative factors in the onset of mental stress ischemia.

Mental Stress and the Onset of Daily Life Ischemia. Just as laboratory-based exercise-induced ischemia is prognostic of daily life ischemia, so to is laboratory-induced mental stress ischemia. For example, a second study based upon the PIMI sample has recently reported that CAD patients with experimentally-induced mental stress ischemia (n=77) had significantly more episodes of daily life ischemia as well as more total time spent in ischemia than did CAD patients without laboratory-induced mental stress ischemia (n=106) (Stone, Krantz, McMahon, et al., 1995; Stone, Krantz, McMahon, et al., 1999). Gottdiener and colleagues (1994) found that CAD patients with new or worsening wall motion abnormalities during laboratory mental stress testing (n=24) also had more episodes of longer duration, low HR ambulatory ischemia than did CAD patients without mental stress ischemia (n=21). Finally, the findings of several studies estimate that roughly 50% of CAD patients with laboratory-induced mental stress ischemia will have episodes of daily life ischemia (Blumenthal et al., 1995; Gottdiener et al., 1994), compared to only about 30-40% of subjects with exercise ischemia (Deanfield et al., 1983; Deanfield et al., 1984b). This difference is likely to be due to the fact that CAD patients with mental stress ischemia appear to have a poorer functional status, considering that they are more likely to have new or worsened wall motion abnormalities during mental stress and exercise testing (Gottdiener et al., 1994), as well as greater hemodynamic responses to laboratory stressors than CAD patients without mental stress ischemia (Blumenthal et al., 1995).

Daily life studies have also reported a link between periods of mental stress and the onset of daily life ischemia. Such studies oftentimes use variations of a previously published and standardized diary system to measure patients' self-report of mental and

physical activities (Hedges, Krantz, Contrada, et al., 1990). For example, a recent study by Gullette and colleagues (Gullette et al., 1997) examined 58 CAD patients with evidence of daily life ischemia as measured by ambulatory ECG, and found that there was a 2.6-3.0 times greater risk for daily life ischemia occurring in the hour after high endorsement of certain negative emotions (i.e., tension, sadness, frustration), than during periods of no endorsement. Adjusted for patients' physical activity levels and the time of day (to control for circadian rhythms), the findings of Gullette et al. (1997) revealed that the risk for mental stress ischemia was still 2.2 times greater after the endorsement of negative emotions than during periods of no endorsement.

Barry and colleagues (1988) also examined the occurrence of ambulatory ischemia with self-reported mental stress in 28 CAD patients, and found that 22% of 372 daily life ischemic episodes occurred during periods of elevated mental stress but usual physical activity. By contrast, 26% of these episodes occurred during periods of elevated physical exertion but usual mental activity. What is more, this study found that, after accounting for the amount of time CAD patients reported spending in various levels of physical and mental activity, the duration of ischemia increased linearly with exertion levels. In other words, this study found that daily life ischemia lasts longer when occurring at higher versus lower physical and mental activity levels (Barry, Selwyn, Nabel, et al., 1988).

Finally, a study by Krantz et al. (1996a) examined 63 CAD patients' self-report of daily life physical and mental activities as related to the onset of myocardial ischemia, and found that 34% of all ischemic episodes occurred during periods of elevated mental activity while 53% occurred during periods of high physical activity. Compared to non-

ischemic periods of the day, Krantz et al. (1996a) found that there was a 1.6 times greater likelihood for experiencing ischemia during periods of high mental stress, a value similar to that reported by Gullette et al. (1997). For physical activity, the risk was 1.9 times greater during periods of heightened exertion. Thus, the findings of both Krantz et al. (1996a) and Gullette et al. (1997) demonstrate that there is roughly a two-fold increased risk for the onset of ambulatory ischemia during periods of elevated mental and physical activity.

Differences Between CAD Patients With and Without Activity-Related Ischemia.

Despite the evidence linking physical and mental activities to the onset of myocardial ischemia, it is still unclear as to why some CAD patients experience daily life ischemia while others do not. Nor is it clear what role physical and mental activities play in delineating who will or will not experience ischemia. While there is some evidence to suggest that CAD patients with and without daily life ischemia do differ, this data is currently weak.

For example, as previously noted, Quigley (2000) found evidence that patients with early morning ischemia had higher levels of physical activity immediately after awakening than did CAD patients without morning ischemia. Although this finding is suggestive, it was not statistically significant and remains tenuous because it was based upon a small sample of subjects. On the other hand, Blumenthal et al. (1995) found that patients with daily life ischemia also had significantly greater hemodynamic responses to laboratory mental stressors than did non-ischemic patients. While noteworthy, in actuality few CAD patients will ever undergo laboratory mental stress testing, therefore, it is difficult to extrapolate such findings to describe the onset of daily life ischemia in the

CAD population at large. Then there are the laboratory findings from PIMI (Goldberg et al., 1996) and Dakak et al. (1995), which suggest that alterations in coronary blood flow due to increases in vascular resistance may distinguish CAD patients with and without mental stress ischemia. In daily life studies, however, coronary resistance is difficult to measure, and because laboratory stressors are contrived, it is likewise difficult to assess whether patients' experiences during experimental settings actually resemble their experiences during daily life. Finally, irrespective of the findings of specific studies, an unresolved complicating factor is the fact that not every period of heightened activity or cardiac workload will result in the onset of ischemia in CAD patients, nor will every period of low activity or workload remain ischemia-free. While the likelihood for ischemia may be greater during periods of heightened mental and physical activity and cardiac workload (Gabbay et al., 1996; Gullette et al., 1997; Krantz et al., 1996a), such conditions do not exclusively predict the onset of daily life ischemia.

Rationale for Investigating Autonomic-Cardiac Regulation in CAD Patients.

Therefore, it may be useful to examine a broader, yet implicit factor commonly related to the development of CAD, changes in physical and mental activity, changes in HR, BP, and coronary blood flow, and the occurrence of myocardial ischemia. As mentioned earlier, autonomic-cardiac regulation, as in the neural regulation of the heart and circulatory system via alterations in sympathetic and parasympathetic efferent activity, is such a factor. For example, the autonomic nervous system (ANS) is largely responsible for the homeostatic regulation of 24-hour HR and BP profiles (Guyton et al., 1996), and is intimately involved in stress-induced changes in HR, BP, systemic, and local blood flow (Ralevic et al., 1993). Furthermore, the ANS is the main neural pathway by which

concerted physical and mental activities exert their cardiovascular and hemodynamic effects. As well, CAD has been found to alter both sympathetic and vagal neuroregulation of the heart (Ahonen, Harkonen, Juntunen, et al., 1975; Airaksinen, Ikaheimo, Linnaluoto, et al., 1987; Bigger et al., 1993; Bigger et al., 1991; Bigger, Fleiss, Steinman, et al., 1995; Burger, 1999; Huikuri, Niemela, Ojala, et al., 1994; Kleiger et al., 1987; Pai, Hu, & Ting, 1995; Zipes, 1990), a condition which has been found by some studies to be an independent predictor of death in post-infarct CAD patients (Bigger et al., 1993; Bigger et al., 1992; Kleiger et al., 1987). Finally, changes in the balance of sympathetic and vagal input to the heart (i.e., \uparrow sympathetic tone, \downarrow vagal tone) commonly coincide with, and immediately precede, the onset of myocardial ischemia (Brouwer et al., 1994; Goseki et al., 1994; Kop et al., 1995; Vardas et al., 1996; Vardas et al., 1994), and usually do not abate until the cessation of ischemia. Thus, it appears that changes in ANS-cardiac neuroregulation influence the relationship between daily life activities, stress-induced changes in cardiovascular and circulatory functioning, and the onset of myocardial ischemia. Therefore, what follows is a detailed discussion on cardiac neuroregulation, its measurement, and its relationship to CAD and the onset of activity-induced ischemia.

Measuring and Interpreting Heart Rate Variability.

An Overview of Autonomic-Cardiac Regulation. The human heart is highly innervated by both branches of the autonomic nervous system, namely, the sympathetic and parasympathetic branches. As a result, the regulation of HR, BP, and overall

cardiovascular functioning will rely upon the interactive influence of these neural axes. For example, normal resting HR levels are maintained by vagal predominance of the heart, with increases in HR resulting from the withdrawal of vagal activity (Guyton et al., 1996). Under stressful conditions or during periods of elevated exertion, however, vagal withdrawal may also be accompanied by increased sympathetic tone (Robinson et al., 1966). This reciprocal relationship between neural axes, in turn, leads to a further augmentation of HR so as to meet the demands of the individual.

ANS control of BP involves several different systems working in tandem in order to maintain BP homeostasis, and to allow active BP responses to new stimuli (Guyton et al., 1996). Furthermore, there is an overwhelming sympathetic predominance in the control of systemic and local blood flow, compared to a subtler vasodilatory role of the vagus. The primary response of the circulatory system to increased sympathetic tone is constriction of peripheral and splanchnic blood vessels and dilation of smooth muscle and coronary blood vessels. As a result of this action there will be an increase in total blood volume and blood pressure, but a decrease in coronary vascular resistance and subsequent increase in coronary blood flow (Guyton et al., 1996).

In patients with coronary artery disease, however, ANS-cardiac deregulation is common and is typified by an overall suppression of efferent autonomic activity, particularly cardiac vagal tone (Bigger et al., 1993; Bigger et al., 1992; Kleiger et al., 1987). For example, previous studies have documented that permanent changes in vagal neuroregulation may result from the heart muscle damage caused by MI (Bigger et al., 1993; Bigger et al., 1992; Kleiger et al., 1987), while other studies have noted transient states of vagal and sympathetic deregulation during episodes of myocardial ischemia

(Brouwer et al., 1994; Goseki et al., 1994; Kop et al., 1995; Vardas et al., 1996; Vardas et al., 1994). Therefore, CAD-related changes in ANS-cardiac neuroregulation may be a causal factor in the onset of adverse coronary events, possibly due to the loss of vagal protection against pro-arrhythmic states.

ANS-cardiac neuromodulation can be measured by heart rate variability (HRV). Subsequently, the following discussion will describe the measurement of HRV in detail, and how it is altered by physical and mental activities. A 1996 joint publication of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology (herein referred to as the "Task Force"), will be the basis for this discussion (Task Force, 1996). Finally, this discussion will conclude with a review of several studies investigating the role of HRV in the onset of MI and ischemia.

Heart Rate Variability. As the name implies, heart rate variability consists of measuring the variance in beat-to-beat HR control as it fluctuates around a person's mean heart rate. Conversely, HRV is not a measure of mean autonomic tone to the heart. Instead, the premise of HRV is that alterations in ANS balance of efferent sympathetic and vagal cardiac tone will result in more or less variation in the interim interval between successive heartbeats. Implicit to this variation of HR, and therefore the estimation of HRV, is the primarily vagal-mediated respiratory sinus arrhythmia (RSA). RSA is the natural fluctuation in HR that occurs with respiration, and results mainly from the "spillover" of autonomic signals from the medullary respiratory center into the vasomotor center (Guyton et al., 1996). In turn, during respiration there is an alternating increase and decrease in the number of sympathetic and vagal impulses transmitted to the sinoatrial

pacemaker of the heart, resulting in the speeding and slowing of HR. This fluctuation is easily detectable in the ECG.

However, in CAD patients, RSA is oftentimes altered as a result of CAD-related changes in cardiac sympathetic and vagal tone (Wolf et al., 1978). These changes will be reflected in the ECG estimation of HRV, and are useful in determining the presence and severity of autonomic-cardiac deregulation. Heart rate variability not only reflects the amount of ANS-cardiac neuroregulation that is imposed by intrinsic physiological control mechanisms, such as respiration (Huikuri, 1995), but also pathological conditions related to disease states.

HRV can also be used to determine the amount of change in ANS-cardiac regulation related to the body's natural response to external demands, such as physical and mental activities. For example, as HR and respiration increase with exertion, respective changes in RSA will reflect the concurrent alteration in parasympathetic and sympathetic input to the heart. What is more, because cardiac vagal tone can be depressed in CAD patients, activity-related changes in HRV can be used to investigate how periods of exertion further alter cardiac neuroregulation, and in particular, cardiac neuroregulation associated with the onset of activity-related myocardial ischemia.

Methods for Analyzing Heart Rate Variability. There are two main methods by which HRV is usually derived from continuous ECG, namely the time domain and frequency domain methods. Time domain methods estimate HRV by relying upon the temporal aspects of ECG data -- as in the heart rate or the interim interval between successive heart beats. Frequency domain methods, on the other hand, are more complex and use power spectral density analyses or autocorrelative analyses to estimate HRV

(also known as power). Depending upon the clinical and/or research questions being asked, there are relative advantages/disadvantages to both methods. The Task Force (1996) has outlined the prevailing circumstances that may make the use of one method's approach preferable to that of the other, as will be discussed next.

Time Domain Analyses. As a standard practice in HRV analyses, each normal-to-normal or "NN interval" is first identified from the 24-hour ECG. The NN interval is the time interval occurring between successive QRS complexes (ventricular depolarizations) that originate from normal sinus node activity (measured in milliseconds). Simple statistics such as the mean NN interval or the standard deviation of all NN intervals (SDNN) can then be calculated on the direct measurement of NN (i.e., instantaneous HR), or on the difference between NN intervals. Furthermore, these values can be derived for an entire 24-hour ECG recording or for recordings of shorter duration. This latter approach allows for HRV comparison between different types of activities (i.e., baseline, task, recovery, etc.), of similar length (i.e., ≥ 2 -5 minutes).

According to the Task Force (1996), SDNN based upon a 24-hour ECG recording represents all cycle components responsible for variability within the recording; that is, 24-hour SDNN is a measure of total power and reflects the combined influence of both neural axes over HR variability. SDNN5, the mean of all 5-minute standard deviations of NN intervals for an entire 24-hour ECG recording, is also a measure of total power that is based upon the variability in HR due to cycle components shorter than 5 minutes. Stated differently, SDNN5 is a "smoothed" total power estimate that utilizes 5-minute aggregate assessments of HRV instead of instantaneous NN variability. A measure of parasympathetic drive to the heart is the square root of the mean squared difference of

successive NN intervals, the so-called, RMSSD. This index is an example of using the mean difference between successive NN intervals to calculate an HRV marker. RMSSD differs from SDSD in that the former is based upon a mean difference in NN intervals as opposed to a difference in contiguous or adjacent NN intervals, as with SDSD. Lastly, SDANN is the standard deviation of the average NN interval calculated over short periods of time, typically 5 minutes.

Index	Units	Description	Measures
SDNN	ms	Standard deviation (SD) of all NN intervals.	Total power
SDANN	ms	SD of the averages of NN intervals in all 5-minute segments of the entire recording.	Sympathetic tone
RMSSD	ms	The square root of the mean of the sum of the squares of differences between adjacent NN intervals.	Vagal tone
SDNN index	ms	Mean of the SD of all NN intervals for all 5-minute segments of the entire recording.	5-minute total power
SDSD	ms	SD of differences between adjacent NN intervals.	Vagal tone
PNN50	%	% of all NN intervals differing by more than 50 ms.	Vagal tone

The SDANN is considered to be a measure of ultra-low frequency variability lasting longer than 5 minutes (i.e., sympathetic tone). A complete list and definition of each standard time domain HRV index can be found in the above table.

As illustrated above, the time domain method for assessing HRV - while relying on nothing more than simple statistics calculated on NN interval variability - generates an array of interrelated indices purportedly reflecting ANS neuromodulation of HR. Because there are so many available indices, the Task Force (1996) recommends using SDNN as

an estimate of 24-hour HRV (total power), SDANN as an estimate of the long-term component of HRV (sympathetic tone), and RMSSD as an estimate of the short-term component of HRV (vagal tone). These recommendations are based upon the favorable statistical properties of each index as derived from 24-hour ECG recordings. Furthermore, the Task Force (1996) recognizes RMSSD as a reliable estimator of vagal tone when based upon shorter spans of time (ECG recordings ≥ 5 minutes). SDNN5 and SDANN are not recommended for recordings of such short duration because these indices tend to be biased towards lower values when derived from smaller samples of NN. As will be discussed next, HRV indices derived from frequency domain analysis are preferred over SDNN5 and SDANN for shorter ECG recordings, due to better statistical properties and a documented physiological basis for these measures.

Frequency Domain Methods. Like time domain analyses, frequency domain analyses of HRV also rely upon the proper determination of the NN interval. This information is submitted to power spectral density analyses (typically fast Fourier transformation), resulting in spectral components of low (0.04-0.15 Hz) and high frequency HRV (0.15-0.40 Hz), among others. For illustrative purposes, Appendix 1 is a power spectral density curve hypothetically derived from a 24-hour ECG recording.

Low Frequency Power. Heuristically, low frequency variability (LF) is considered to be a measure of sympathetic drive to the heart, but there is evidence to suggest that LF may also reflect some degree of vagal cardiac modulation as well. In other words, LF is probably not a "pure" measure of sympathetic tone when considered in absolute units (i.e., in milliseconds). However, when expressed in normalized units, as in the ratio of LF relative to total power, LF is considered by most experts to be a discrete

measure of sympathetic cardiac drive. For instance, several studies have shown that activities which would typically be expected to increase sympathetic drive to the heart as well as increase HR, such as physical exertion and erect posture (Huikuri et al., 1994), or mental stress (Kral, Becker, Blumenthal, et al., 1997), in fact do so as evidenced by an increased normalized LF and higher HR values. Thus, any discussion of LF henceforth will be in regard to cardiac sympathetic neuromodulation.

High Frequency Power. High frequency variability (HF), on the other hand, is considered to be a relatively pure measure of parasympathetic or vagal input to the heart. As mentioned earlier, it is widely believed that resting HR is mainly controlled by vagal regulation, thus changes in HF will reflect this control. For example, paced breathing protocols in which subjects respire 10-20 times a minute while resting is a documented method of increasing vagal predominance. Paced breathing results in higher normalized values of HF (Airaksinen et al., 1987). Other techniques, such as exposing one's face to cold temperatures, or tilt-table rotation, or use of beta-adrenergic blocking agents also lead to an increase in normalized HF values, again by increasing vagal input to the heart (Malliani, Pagani, Lombardi, et al., 1991; Pagani, Lombardi, Guzzetti, et al., 1986). Finally, nocturnal sleep is a classic example of vagal predominance due to the lack of concerted physical and mental activities; in healthy individuals, HF is usually highest during this time of the day (Huikuri, Kessler, Terracall, et al., 1990; Huikuri et al., 1994).

Sympathovagal Tone. Because of the reciprocal relationship between LF and HF (i.e., as LF increases, HF decreases and vice versa), the ratio of LF/HF, called "sympathovagal tone (or balance)", is a useful estimate of the concurrent and relative influence of both neural axes in controlling the heart, especially when illustrated in

normalized units. For instance, using nocturnal sleep as an example again, heightened levels of vagal tone but minimal levels of sympathetic tone are typical during deep sleep (Degaute, van de Borne, Linkowski, et al., 1991), and result in a reduction in sympathovagal tone. On the other hand, morning awakening is associated with a dramatic shift towards sympathetic predominance and vagal withdrawal as a result of the body preparing itself for the beginning of a new day (Furlan, Guzzetti, Crivellaro, et al., 1990). In this case, sympathovagal tone will increase. Again, sympathovagal tone is a useful temporal marker of the reciprocal predominance of sympathetic and vagal input to the heart.

Special Considerations Affecting HRV Estimates. Besides LF, HF, and their ratio, it is also possible to derive ultra-low frequency (ULF; < 0.003 Hz), very low frequency (VLF; 0.003-0.04 Hz), and total power estimates ($< .40$ Hz) from spectral analysis of 24-hour ECG recordings. However, because the physiological bases for ULF and VLF are not well defined, the Task Force (1996) does not recommend their use beyond exploratory research purposes. Likewise, the Task Force (1996) advises against using a spectral total power estimate of HRV since this approach is based upon the statistical assumption of HR "stationarity". That is, since HR will fluctuate during a 24-hour ECG recording (i.e., will not be stationary), an important statistical assumption of spectral analysis will be violated and may result in a biased estimate of total power. Instead, the Task Force (1996) recommends using SDNN as a substitute estimator of 24-hour total HRV. However, HR stationarity is less of a limiting factor for LF, HF, and LF/HF since these indices are usually used to estimate HRV during shorter spans of time (i.e., ≥ 2 -5 minutes of task), when HR is more stable.

Besides the assumption of HR stationarity, there are several other factors that can affect the accuracy of HRV estimation which need to be considered. Most important are those factors that can affect the proper identification of the NN interval, since both methods of HRV estimation rely upon accurate NN determination for their analyses. For example, certain arrhythmias such as atrial fibrillation or flutter can affect HRV estimation via altered ECG morphology and irregular HR. As well, prolonged QT syndrome can reduce the reliability of NN interval identification due to changes in the length of ventricular depolarization. In other words, any circumstances that can affect conduction speed can greatly affect HRV accuracy and could be considered exclusionary criteria for HRV interpretation.

On the other hand, medical procedures such as coronary artery bypass grafting (Demirel, Tukek, Akkaya, et al., 1999; Kuo, Chen, Lai, et al., 1999) or heart transplantation can also reduce HRV immediately post-procedure, with transplantation usually resulting in a permanent autonomic changes as a result of cardiac denervation. Cardioactive medications such as beta-adrenergic blocking agents or digitalis alter ECG morphology and rate, but may also cause artificial shifts in autonomic balance due to their anti-arrhythmic effects. Lastly, certain disease states, particularly Type I diabetes mellitus, may cause central changes to autonomic tone as a result of diabetic neuropathy.

Finally, there are also technical factors to consider when estimating HRV from ECG recordings. Previous studies have shown that ECG recordings shorter than 24-hours will cause SDNN to estimate shorter and shorter cycle lengths, resulting in an imprecise reduction in total HRV estimation (Saul, Albrecht, Berger, et al., 1988). Therefore, it is important to compare SDNN measurements obtained from ECG recordings of equal

length. As well, the quality of the ECG recording will greatly effect both the reliability and validity of HRV estimation for obvious reasons.

In summation, while there are certain restrictions to consider when measuring HRV, it is still a very useful research tool, and makes possible the non-invasive investigation of altered cardiac neuroregulation resulting from physiological, behavioral, emotional, and disease states. As well, HRV aids in the risk stratification of patients who are susceptible to fatal arrhythmic conditions and provides researchers with a somewhat complicated yet novel "window on the brain" regarding cardiac neuroregulation. Before discussing the rationale for measuring HRV in the current study, however, it is necessary to review previous investigations of HRV in CAD patients, as well as to discuss the alteration of HRV by physical and mental activities.

Alterations in Heart Rate Variability with Coronary Artery Disease.

Disturbances in myocardial electrical activity co-occur with the perfusion defects characteristic of myocardial infarction and ischemia. These states of electrical instability can be permanent, as with the death of viable cardiac tissue after an MI, or transient, as in the case of episodic myocardial ischemia. More importantly, however, such disturbances in electrical conductance translate into altered ECG data, particularly the respiratory sinus arrhythmia, which is integral to HRV estimation. Consequently, the occurrence of CAD-related phenomena such as MI and ischemia will result in telltale changes in HRV, allowing researchers to examine the relative contribution of sympathetic and vagal input to the heart during adverse cardiovascular events.

Myocardial Infarction and Reduced Heart Rate Variability. Heart muscle death resulting from myocardial infarction can result in collateral damage to nerve fibers traversing the zone of necrotic tissue (Ahonen et al., 1975). This nerve damage will result in altered HRV, as evidenced by changes in the vagally-mediated RSA component of the ECG (Wolf et al., 1978). Although HRV begins to stabilize within the first few months after an MI, it usually does so at lower than normal levels (Bigger et al., 1991). Therefore, survivors of acute MI face an increased risk for death from deranged autonomic control, not to mention from the progression of their underlying atherosclerotic disease.

The first large-scale, prospective study of HRV as a predictor of mortality in post-infarct CAD patients was performed by Kleiger and colleagues (1987). This investigation examined pre-discharge ECG recordings of 808 recent MI patients, and found that patients with SDNN (total power) less than 50 ms. had a fourfold increased risk for death in the ensuing four year follow-up period than did patients with SDNN greater than 100 ms. Patients with SDNN between 50-100 ms. were roughly one and a half times more likely to die than patients with SDNN greater than 100 ms. After statistically adjusting for a number of clinical, demographic, and cardiovascular risk factors, patients with HRV less than 50 ms. were still almost three times more likely to have died during the four year follow-up period than were patients with HRV greater than 50 ms. Hence, the findings of Kleiger et al. (1987) clearly demonstrate a dose-dependent increase in the risk for death related to reduced HRV in post-infarct patients. These findings have since been replicated by numerous other studies (Algra, Tijssen, Roelandt, et al., 1993; Bigger et al.,

1993; Bigger et al., 1992; Copie, Hnatkova, Staunton, et al., 1996; Farrell, Bashir, Cripps, et al., 1991; Rich, Saini, Kleiger, et al., 1988).

While lower pre-discharge HRV may predict death in CAD patients who are immediately post-infarct, the question remains as to whether or not HRV measured late after an MI is also predictive of death in CAD patients. In a study by Bigger and colleagues (Bigger et al., 1993), HRV was measured in 331 post-MI patients one year after their heart attacks to see if HRV predicted all-cause mortality in the ensuing two-year follow-up period. A total of 30 patients died during follow-up and the results of univariate analyses showed that the risk of death was significantly higher in CAD patients with reduced HRV. Specifically, in patients with lower total HRV as well as lower vagal tone, the risk of death was roughly three and a half times greater than in patients with relatively higher index values. In addition, reduced LF conferred over a five and a half times increased risk for death, while the risk for death related to a reduced LF/HF ratio was two and a half times greater. Multivariate analyses adjusted for a number of known post-MI risk factors did not drastically alter these risk ratios, which ranged from 2.8 to 5.4. Therefore, similar to the findings of Kleiger et al. (1987), the findings of Bigger et al. (1993) demonstrate a substantial increased risk for death related to reduced HRV in post-infarct CAD patients, even when HRV is measured well after the occurrence of MI.

Uncomplicated CAD and Reduced Heart Rate Variability. It is still unclear as to whether or not the presence of atherosclerotic disease *per se* is sufficient to lead to chronic HRV changes in patients with uncomplicated CAD (i.e., no previous MI). Unlike post-infarct alterations in autonomic tone, there is no heart muscle death with

uncomplicated CAD. What is more, the role of cardiac denervation due to ischemic conditions has only recently been examined in this patient sample (Hartikainen, Mustonen, Kuikka, et al., 1997). Thus, evidence of altered HRV in patients with uncomplicated CAD may represent a prodromal state of autonomic deregulation related solely to the presence of atherosclerosis.

For example, in a recent study by Burger and colleagues (1999), the 24-hour HRV of CAD patients was compared to that of healthy subjects, as well as to patients with Type I diabetes mellitus. Results from this study showed that all spectral as well as time domain indices of HRV (except SDNN5) were significantly reduced in the two patient samples (Burger, 1999). This study, however, included some CAD patients with previous MI (26.0% of CAD sample), so these results may be nothing more than a reiteration of previous study findings. Consequently, Huiruki and associates (1994) compared the HRV of 20 male patients with uncomplicated CAD to that of 20 male controls, and found no significant difference in any of the 24-hour indices of HRV, with the exception of a significant reduction in vagal tone during sleep in the CAD group. On the other hand, the overall data trend indicated that HRV indices were generally lower in CAD patients. More importantly, however, this study showed that whereas normal subjects had a significant circadian rhythm in HF, LF, and HF/LF ratio, with higher levels of vagal tone during sleep and higher levels of sympathetic tone during the day, CAD patients did not. Instead, CAD patients had a blunted rhythm in all indices, which along with a significantly lower vagal tone during sleep, indicates that HRV may be deranged in CAD patients irrespective of MI status.

As mentioned earlier, paced breathing exercises in which people respire deeply (> 40% of capacity) and slowly (10-20 breathes/minute) while resting, is a standard non-invasive technique for assessing vagal integrity. A study by Airaksinen and associates (1987) compared the results of deep breathing exercises for CAD patients and healthy controls and found that vagal-mediated HR changes during deep breathing (i.e., RSA) were significantly lower in patients with CAD. This finding again suggests that vagal modulation of HR is altered in patients with CAD. However, this study also found that changes in vagal tone did not differ in regard to the extent of CAD or its severity (Airaksinen et al., 1987). Specifically, there were no significant differences in HRV related to the number of diseased vessels, left ventricular function, or New York Heart Association classification of CAD severity. Other studies have also failed to find an association between the extent and severity of CAD and the attenuation in vagal activity, suggesting that the presence of CAD *per se* may be sufficient to lead to disturbances in autonomic tone (Pai et al., 1995).

Besides possible CAD-related changes in vagal tone, uncomplicated CAD also appears to affect sympathetic control of the heart as well. In an ingenious study by Hartikainen and associates (1997), patients with uncomplicated CAD underwent a symptom-limited dual radioisotope exercise protocol designed to assess the extent of ischemic myocardium, as well as the extent of sympathetic cardiac denervation of the left ventricle (LV) during ischemia. CAD patients with a previous infarct were used for comparison. The results of this study showed that all but one patient with uncomplicated CAD presented with sympathetic denervation during ischemia (Hartikainen et al., 1997). In fact, this area of LV sympathetic denervation was found to be significantly larger than

the average regional defect related to ischemic myocardium. Stated differently, the collateral sympathetic denervation during myocardial ischemia actually exceeded the area of myocardial tissue under its control. What is more, patients with more severe coronary blockages ($> 90\%$ of luminal diameter) had even larger areas of LV denervation, while the size of post-MI patients' sympathetic and ischemic defects was greatest. In other words, this study found that LV sympathetic denervation related to myocardial ischemia actually worsens with the severity of CAD. In turn, these findings imply that sympathetic nervous tissue is more sensitive to the effects of ischemia than is myocardial tissue, and documents yet another possible etiology for CAD-related changes in HRV.

Contrary Findings. Although the above studies report that CAD patients have altered HRV as compared to healthy individuals, findings in this area are not conclusive. For example, a recent study by Pai and colleagues (1995) failed to find differences in 24-hour HRV when comparing patients with uncomplicated CAD to healthy controls. Like the findings of Huikuri et al. (1994), 24-hour time domain and spectral HRV indices were similar between patients with significant CAD, CAD patients with minimal disease, and healthy controls (Pai et al., 1995). Then again, this study did not examine, and may therefore have missed, the circadian differences in HRV that purportedly differentiates CAD patients from healthy individuals (Huikuri et al., 1994). More importantly, however, this study showed that there were no significant differences in HRV among CAD patients with varying levels of atherosclerotic disease (i.e., number of diseased vessels), a finding supported by other studies as well (Rich et al., 1988). Therefore, while some studies have found changes in HRV in patients with uncomplicated CAD, other

studies have not. Thus, it remains unclear as to what extent underlying atherosclerotic disease affects HRV in patients with uncomplicated CAD.

Changes in HRV with Myocardial Ischemia. Several studies have provided clear and consistent findings to suggest that HRV is transiently altered with the onset of myocardial ischemia. For example, Goseki and colleagues (1994) examined HRV changes related to the onset of 33 ischemic events in 19 CAD patients with stable disease, and compared this data to non-ischemic control periods of similar HR, as well as to baseline HRV measurements taken from the same individuals. Compared to baseline HRV, Goseki et al. (1994) found that vagal tone significantly decreased before the onset of ischemia, beginning about 10 minutes before the onset of the event. On the other hand, there were no significant changes in vagal tone during non-ischemic control periods. In addition, there were no significant changes in pre-ischemic HR, although onset HR levels were elevated over baseline measurements. However, sympathovagal tone (LF/HF) was significantly higher during the thirty minutes before ischemia, suggesting that sympathetic tone was elevated in addition to the observed withdrawal of vagal activity. Thus, the findings of Goseki et al. (1994) demonstrate that a significant withdrawal in vagal tone immediately precedes the onset of myocardial ischemia, during a period of elevated sympathetic activity. This sequence of events is similar in nature and time-course to that observed with the onset of acute myocardial infarction (Webb, Adgey, & Pantridge, 1972).

Similarly, Brouwer and colleagues (1994) investigated the time-course of HRV changes occurring immediately before and after the onset of 33 ambulatory ischemic events in 14 patients with stable CAD. During the thirty minutes before ischemia,

sympathetic tone increased while vagal tone decreased. HR as well as sympathovagal tone also increased before the onset of ischemia. During the actual ischemic event, these indices reached their respective highest or lowest values. Conversely, during the thirty minutes after ischemia, vagal tone began to increase, while sympathetic tone, HR, and sympathovagal balance decreased. Again, these findings show a clear disruption in cardiac neuroregulation surrounding the onset of daily life ischemia.

Finally, Vardas and colleagues (1994, 1996) investigated the time-course of HRV changes specifically related to the onset of nocturnal ischemia, a time of day when vagal activity is predominant, in 15 patients with uncomplicated CAD. Similar to the findings of Goseki et al. (1994), these researchers found that a significant withdrawal in vagal activity began about 10 minutes before the onset of ischemia, while sympathovagal tone increased. Sympathetic tone also began to rise during this period, but not significantly. Like the findings of Brouwer et al. (1994), Vardas et al. (1994) found that sympathetic tone and sympathovagal balance reached their respective lowest or highest values around the actual start of the ischemic event.

Collectively, these findings document that a transient withdrawal in vagal activity consistently precedes the onset of myocardial ischemia, concurrent to somewhat elevated levels of sympathetic tone. These changes in autonomic-cardiac tone are likewise related to elevated HR levels. However, because the cited studies failed to measure patients' physical or mental activities co-occurring with their changes in HRV and HR, it is unclear if these changes were related to, or independent from patients' activities. Therefore, the following discussion details how physical and mental activities *per se* can

lead to changes in HRV that may be conducive to the onset of myocardial ischemia in patients with CAD.

Alterations in Heart Rate Variability During Activities and Activity-Related Ischemia.

The Effect of Physical Activity on Heart Rate Variability. In most individuals, moderate increases in physical activity levels, as with light exercise, will result in an immediate increase in HR, primarily through withdrawal of vagal tone. For example, Fagraeus and Linnarsson (1976) showed that a peak in HR occurred about 10 seconds after the start of light exercise in 6 healthy men (i.e., bicycle pedaling at 50 watts), followed by a brief (~ 7 second) transient reflexive deceleration in HR. This deceleration was subsequently followed by a stable re-elevation in HR of around 21 bpm, which endured throughout the task. The role of vagal mediation in this time-course of HR changes was established by the fact that vagal blockade by atropine (2.0-2.5 mg. or 0.03 mg/kg body weight) completely abolished this pattern of HR changes, whereas adrenergic blockade with propranolol (10 mg. or 0.15 mg/kg body weight) had no effect. Thus, vagal regulation of HR is predominant not only for resting HR levels, but the findings of Fagraeus and Linnarsson (1976) suggest that the vagus has predominant control over HR during periods of light physical exertion as well.

At higher levels of exertion, however, vagal withdrawal is also accompanied by increased sympathetic activity, so as to increase HR to meet the needs of the individual (Guyton et al., 1996). For example, in a study by Robinson and colleagues (1966), 4 healthy male subjects engaged in a treadmill exercise protocol of steadily increasing

difficulty while under sympathetic blockade, vagal blockade, dual blockade, and control conditions. Oxygen consumption as well as HR were continuously measured on all study days as indicators of overall workload. Interestingly, with sympathetic blockade with propranolol (0.25 mg/kg body weight), HR responses were generally lower or equal to HR responses during the control exercise protocol. However, at the highest stages of exercise, the HR of 3 of 4 subjects was lower during sympathetic blockade than during the same stages of exercise in the control protocol. Oxygen consumption, on the other hand, was similar at each exercise stage during both conditions, suggesting that similar levels of workload were reached. During vagal blockade with atropine (2.0 mg), the HR of all subjects was significantly higher at all stages of exercise than during sympathetic or dual blockade, or during control conditions. With vagal blockade, baseline HR was also elevated compared to the control condition, and again, oxygen consumption levels with exercise were similar. Thus, the findings of Robinson et al. (1966) not only reaffirm the role of the vagus in controlling resting HR levels, but also demonstrate that at higher levels of physical activity, vagal control is augmented by increased sympathetic input to the heart.

Although the studies cited above were conducted in healthy individuals, their findings nonetheless highlight several important facts regarding physical activity and ANS neuromodulation of HR that may have important consequences for patients with CAD. Perhaps the most intriguing finding is the fact that activity-induced changes in HRV and HR in normal subjects actually mimic the changes in HRV and HR observed during the onset of myocardial ischemia in patients with CAD. For example, Fagraeus and Linnarsson (1976) showed that a moderate increase in physical activity was related to

an immediate decline in vagal tone and significant increase in HR. In turn, this decline in vagal activity and increase in HR parallels the vagal withdrawal and increase in HR observed by Goseki et al. (1994) and others (Brouwer et al., 1994; Vardas et al., 1994, 1996) before the onset of ischemia. Furthermore, the immediacy of these changes with the onset of physical activity suggests that, in CAD patients, physical activity may trigger ischemia via acute shifts in cardiac workload related to rearranged vagal and sympathetic activity. Stated differently, these findings suggest that in CAD patients, it is possible that activity-related changes in HRV may mediate the relationship between physical activity, increased levels of myocardial oxygen demand, and the onset of myocardial ischemia.

Second, the findings of Robinson et al. (1966) showed that decreased vagal but increased sympathetic input to the heart are typical during physical exertion. This reciprocal shift in autonomic tone with increased physical activity is similar to the changes in HRV that occur during the onset of myocardial ischemia. Moreover, the involvement of sympathetic neuronal activity in the onset of myocardial ischemia has been documented in both angiographic as well as laboratory-based studies of exercise-induced ischemia, and is also quite sensitive to the effects of ischemia (Hartikainen et al., 1997). Thus, the findings of several studies provide clues to suggest that, in CAD patients, the onset of activity-induced ischemia may be due to ANS-mediated changes in myocardial oxygen demand requirements (Fagraeus et al., 1976; Robinson et al., 1966).

Physical Activity, Changes in Heart Rate Variability, and the Onset of Daily Life Myocardial Ischemia. Despite the similarities outlined above, there is no conclusive evidence that activity-induced changes in HRV in normal subjects are the same as HRV changes which occur with the onset of ischemia in patients with CAD. Moreover, there is

a dearth of scientific investigation specifically examining physical activity-induced changes in HRV and the onset of ischemia in CAD patients. However, one study by Hayano and colleagues (1994) did recently investigate this relationship by examining the autonomic neuroregulation of HR before and during the onset of 91 ambulatory ischemic episodes (60 of which were activity-related), in 28 patients with documented CAD. In turn, this study found that with activity-related ischemia there was a pre-ischemic increase in both HR and sympathovagal tone concomitant to a decrease in vagal input to the heart (Hayano, Wei, Mukai, et al., 1994). These changes were noted to occur anywhere from 7-19 minutes prior to the onset of ischemia. Conversely, for resting ischemia, only sympathovagal tone increased before the onset of ischemia, beginning about 3 minutes before the onset of the event. During both activity-related and resting ischemia, however, there was a significant increase in HR without a corresponding change in vagal activity. Furthermore, an inverse shift in sympathovagal tone occurred during ischemia, increasing during resting ischemia but decreased during activity-related ischemia. Because of the scarcity of studies like Hayano et al. (1994) these findings will be reviewed in detail.

First, the fact that both HR and sympathovagal tone increased before activity-related ischemia while vagal activity decreased suggests, according to the authors, that physical activity was predominantly responsible for the observed pre-ischemic increase in cardiac demand, via alterations in autonomic tone. If true, this finding could explain similar observations reported by Goseki et al. (1994) and others (Brouwer et al., 1994; Vardas et al., 1994, 1996), regarding the changes in HR and HRV before the onset of ischemia.

On the other hand, what is less straightforward is why significant increases in HR occurred during ischemia, regardless of activity level, when no further changes were observed in vagal activity. For resting ischemia, this increase in HR can be explained by increased sympathetic activity, as indicated by elevated levels of sympathovagal tone during ischemia. However, during activity-related ischemia, sympathovagal tone actually decreased. When combined with the fact that there were no observed changes in vagal activity during ischemia, this finding suggests that there may have actually been a withdrawal in sympathetic input to the heart during these events. In turn, this finding not only fails to explain the observed increase in HR during activity-related ischemia, but is also counterintuitive. Then again, another possibility is that this finding was spurious⁵. Still, the findings of Hayano et al. (1994) highlight the role of the ANS in mediating the hemodynamic effects of physical activity with the onset of daily life ischemia.

While not specifically addressing the onset of myocardial ischemia, the findings of Huiruki et al. (1994) provide additional insight into how individuals with and without CAD differ regarding activity-related changes in autonomic tone. Specifically, this daily life study investigated the effects of morning awakening and upright posture on HRV changes in 20 male patients with uncomplicated CAD, and compared these results to a group of 20 male healthy controls. As part of their participation, all subjects were asked to remain in bed for 30 minutes after awakening so that the central effects of awakening on HRV could be analyzed separately from those related to postural changes and the

⁵ Since HRV units were not reported in this abstract (i.e., milliseconds² vs. normalized units), it is possible that the observed change in sympathovagal tone during ischemia could decrease in value when expressed in milliseconds, but increase in value when expressed in normalized units. However, the authors provide insufficient information for making such a determination.

initiation of daily activities. In turn, the findings from this study showed that in healthy subjects, morning awakening resulted in a decrease in vagal tone, an increase in sympathetic tone, and an increase in HR. Sympathovagal tone also increased after awakening in control subjects. In patients with uncomplicated CAD, however, morning awakening had no significant effect on vagal or sympathetic activity, sympathovagal tone, or HR. However, postural changes and the initiation of physical activities resulted in a significant decrease in vagal activity and an increase in sympathovagal balance and HR in both groups of subjects. Thus, the findings of this study not only demonstrate that daily life activities can lead to changes in autonomic control of HR, but that the autonomic response of patients with uncomplicated CAD appears to be muted to central stimuli, but normal in regard to exogenous stimuli. In terms of myocardial ischemia, the findings of Huiruki et al. (1994) hypothetically suggest that the morning peak in daily life ischemia may be induced, in part, by a deranged autonomic-cardiac response by CAD patients to the initiation of daily life activities upon arising.

The Effect of Mental Activity on Heart Rate Variability. As previously discussed, mental stress results in a significant sympathoadrenomedullary response characterized by increased levels of HR and BP. Consequently, changes in HRV during periods of heightened mental activity are similar to those occurring during physical activity, namely vagal withdrawal and increased sympathetic input to the heart. For example, in a recent study by Bernardi and colleagues (2000), the relationship between mental activities and HRV was examined in a sample of 12 healthy individuals. As part of their participation, subjects were asked to perform a number of different mental tasks, including mental arithmetic, while under time pressure by staff. Compared to baseline values, the results of

this study showed that mental stress led to an increase in HR, SBP, as well as diastolic BP (DBP) (Bernardi, Wdowczyk-Szulc, Valenti, et al., 2000). As expected, mental stress was also related to a significant decrease in vagal tone, and a trend towards higher levels of sympathetic tone. Similarly, Ring and colleagues (2000) have reported that during mental arithmetic, the HR, SBP, and DBP of 23 healthy individuals were observed to increase concomitant to a significant decrease in vagal activity and significant increase in sympathetic activity (as measured by pre-ejection period) (Ring, Harrison, Winzer, et al., 2000). Several other studies have also reported changes in HRV and cardiac demand with the onset of mental stress in patients with and without coronary artery disease (Bernardi et al., 2000; Kop et al., 1995; Kral et al., 1997).

Mental Stress, Changes in Heart Rate Variability, and the Onset of Myocardial Ischemia. The autonomic and hemodynamic response of CAD patients to mental stress testing is similar to that for healthy subjects, but there is evidence to suggest that some fundamental differences may exist. For example, in a study by Kral and associates (Kral et al., 1997), 152 siblings of patients with premature coronary heart disease underwent laboratory exercise stress testing prior to, as well as ambulatory ECG monitoring during mental stress testing. In turn, 15 subjects were found to have had an ischemic response to exercise, of whom 11 were later found to have had moderate levels of coronary disease. Consequently, Kral et al. (1997) compared this ischemic subgroup to the remaining sample with regard to their autonomic and hemodynamic response to mental stress testing.

Interestingly, while all non-CAD siblings were found to have elevated HR and BP to mental stress testing (Stroop Word-Color task), patients with exercise ischemia were

noted to have significantly greater SBP and DBP responses to mental stress by comparison. HR responses were also higher in the ischemic subgroup, but not significantly. Furthermore, the results of HRV analyses showed that patients with exercise ischemia had significantly higher levels of sympathetic tone during mental stress testing than did healthy subjects, but neither group differed regarding changes in vagal tone. Thus, the findings of Kral et al. (1997) illustrate the fact that, in individuals with a high risk for developing coronary disease, there is a strong relationship between cardiovascular reactivity to mental stress and exercise-induced myocardial ischemia. Moreover, this hemodynamic response appears to be related to exaggerated sympathetic reactivity to mental stress in moderately diseased CAD patients. In other words, differences in autonomic as well as hemodynamic responses to mental stress appear to differentiate subjects with and without evidence of exercise-induced myocardial ischemia.

Finally, regarding ambulatory ischemia, Kop and associates (1995) investigated the relationship between self-reported mental stress levels and changes in vagal activity preceding the onset of 31 episodes of daily life ischemia in 13 men with CAD. Thirty-one HR-matched non-ischemic control periods were identified and used for comparison. As expected, Kop et al. (1995) found that self-reported mental stress levels were significantly higher before the onset of daily life ischemia than during non-ischemic control periods. Similar to the findings of laboratory studies, these researchers also found that a withdrawal in vagal activity preceded the onset of daily life ischemia, and was inversely related to pre-ischemic mental stress ratings (Kop et al., 1995). Finally, the results of regression analyses showed that self-reported mental stress was an independent

predictor of vagal activity. Thus, the findings of Kop et al. (1995) suggest that mental stress-related changes in vagal activity may trigger the onset of daily life ischemia.

Summary and Rationale.

By investigating the changes in HRV that occur with specific behavioral, emotional, and/or disease states, the findings of previous studies have highlighted the importance of the ANS in regulating the human cardiovascular system. For example, besides its role in maintaining cardiovascular homeostasis, the ANS is also intimately involved in mediating stress-induced changes in function, as discussed. On the other hand, pathological changes in ANS-cardiac neuroregulation can also occur, and are oftentimes the end product of coronary disease. Therefore, because the ANS is so pervasive in the regulation of human physiology - and is itself susceptible to change from pathological and biobehavioral influences - more and more researchers are choosing to employ HRV as a means of precisely exploring the details of ANS-cardiac neuroregulation.

Study Overview, Objectives, and Hypotheses.

Study Overview. This study measured CAD patients' physical and mental activities, heart rate variability, heart rate, and blood pressure during 48-hours of daily life monitoring. Patients' self-reported physical and mental activities were assessed via a previously validated and published structured diary system (Hedges et al., 1990), while

patients' ambulatory physical activity, HR, HRV, and BP levels were measured through use of ambulatory monitors.

Study Objectives. This study had two main objectives. The first objective was to determine whether or not there were differences between CAD patients with and without daily life ischemia in terms of their autonomic and hemodynamic stress response to various levels of daily life physical and mental activity. The second objective was to examine whether or not the relationship between physical activity and cardiac demand levels related to the onset of ambulatory ischemia was likewise related to pre-ischemic changes in HRV.

HYPOTHESES

- 1) It is predicted that CAD patients with lower 24-hour HRV (SDNN), and in particular vagal tone (RMSSD), will have significantly higher 24-hour HR and BP levels as well as more episodes of daily life ischemia than will CAD patients with higher HRV indices.
- 2) During non-ischemic periods of matched low and high physical activity, ischemic CAD patients will have significantly lower levels of cardiac vagal tone (HF), significantly higher sympathovagal balance (indicative of reduced vagal tone), and significantly higher levels of HR and BP compared to non-ischemic CAD patients.

- a) It is likewise predicted that the shift in cardiac vagal tone, sympathovagal balance, HR, and BP from low to high periods of exertion will be greater for ischemic CAD patients than for non-ischemic patients.
- 3) Regarding ambulatory ischemia, it is predicted that there will be a significant pre-ischemic decrease in cardiac vagal control (HF) and significant increase in sympathovagal tone (LF/HF), HR, and BP concurrent to pre-ischemic changes in physical activity.

METHODS

Subjects. The sample for this study included 55 patients with documented coronary artery disease as determined by angiography, prior myocardial infarction, or positive exercise stress test. These volunteers were recruited from the National Naval Medical Center (NNMC), Bethesda, Maryland. The inclusion/exclusion criteria for volunteer selection were:

INCLUSION CRITERIA

Documented coronary artery disease
Freely ambulating volunteers
35-80 years of age

SOCIODEMOGRAPHIC EXCLUSION CRITERIA

Shift Worker
< 35 or > 80 years of age
Sleep disturbances
Current Psychiatric Problems

MEDICAL EXCLUSION CRITERIA

Resting ST segment depression
Unstable Angina
Previous coronary artery bypass graft
Pacemaker assistance
Myocardial infarction within 3 months of participation
Coronary angioplasty within 6 months of participation
Coronary stenting within 12 months of participation
Left Ventricular Hypertrophy
Left Bundle Branch Block
Chronic Obstructive Pulmonary Disease
Digitalis medication

The use of these criteria assured that no extraneous factors influenced the measurement of physical activity (e.g., shift work, sleep disturbances, psychomotor disturbances related to psychopathology), or precluded the accurate measurement of HRV or activity-related ischemia (e.g., medical exclusions). The medical histories of all possible volunteers were screened before the research staff solicited their participation by phone.

Procedure. This study consisted of 48-hours of daily life monitoring in which patients with known CAD were asked to wear three small non-invasive monitors. These monitors included a physical activity monitor or actigraph, as well as an ambulatory ECG (Holter) monitor, and ambulatory blood pressure monitor (ABPM) (see Appendix 2 for diagram of monitor placement). Participants also completed a structured self-report diary throughout their monitoring (see Appendix 3 for an example of a structured diary page), in addition to psychosocial questionnaires not related to the current study. No changes were made to patients' medication regimens during this study, and a cardiologist and research staff member monitored volunteers during their participation. At the end of the study, all research materials were returned to staff via pre-paid parcel service (i.e., Fed

Ex□), and volunteers received \$50.00 for their participation (Active duty volunteers did not receive remuneration for their participation in this study).

Eligible CAD volunteers who were interested in participating in this study were asked to make one visit to NNMC for witnessed, informed consent, instrumentation with the monitors, and 10 minutes of baseline activity, HR, and BP measurements. Participants then began their 48-hour ambulatory monitoring period and completed the structured diary system as described below. The figure below illustrates the estimated study timeline.

Projected Study Timeline.

Initial Visit	Day 1	Day 2	End of 48-hours	Conclusion
1) Informed consent 2) Instrumentation 3) 10 min. baseline measurements 4) Begin 48-hour monitoring	1) 2-3 diary entries/daytime hours (42 max.) 2) Complete Psychometric Surveys	1) 2-3 diary entries/daytime hours (42 max.)	1) Removal of instruments and collection of materials for return to researchers (via Fed Ex□)	1) Mailed \$50.00 check
60 minutes	~ 1.25 hours	~ 45 minutes	~ 10 minutes	

Instrumentation.

Ambulatory ECG monitoring. Participants were asked to wear a three-lead ambulatory ECG monitor (Series 8500, Marquette Medical Systems; Milwaukee, Wisconsin) for 48-hours of daily life. Seven small adhesive electrodes were positioned on

the patient's chest, corresponding to a modified V5, V1, and aVF position. These electrodes were then connected to the monitor via small wires. The size and weight of this monitor was equivalent to that of a "Walkman" radio, and was worn on a belt around the patient's waist (see Appendix 2).

Each ECG monitor was automatically calibrated at the beginning of each recording (1 mV = 10 mm). An ischemic response was defined as horizontal or downsloping ST segment depression ≥ 1.0 mm below the isoelectric baseline, occurring 0.08 seconds after the J point and persisting for at least 60 seconds. A blinded cardiologist interpreted all ECG data generated by this study. ECG analyses were conducted at an external core lab located at Brigham and Women's Hospital in Boston, Massachusetts.

The indices derived from participants' ECG monitoring included the number, time, and duration of each recorded episode of ischemia, as well as the mean, peak, and onset HR for each episode. Minute-to-minute, as well as mean, maximum, and minimum hourly HR were also provided for the entire 48-hour monitoring period. In addition, ECG analyses included 24-hour total power estimates of HRV (SDNN) and vagal tone (RMSSD), as well as spectral indices of vagal (HF), sympathetic (LF), and sympathovagal tone (LF/HF) for each ischemic episode, as well as for each of the non-ischemic comparisons periods outlined in the hypotheses. These HRV indices were described earlier.

Ambulatory BP monitoring. Simultaneous 48-hour BP monitoring was performed by the arm-cuff method, using a Space Labs[®] model 90207 ambulatory blood pressure

monitor (Spacelabs Medical, Inc., Redmond, Washington). The blood pressure cuff was positioned on the upper portion of participants' non-dominant arms and the monitor was worn on a belt around the patient's waist. The dimensions of this device were the same as the ECG monitor.

For this study, the BP monitor was synchronized to the ambulatory ECG and activity monitors, providing simultaneous measurements of physical activity, HR, and BP. Blood pressure assessments occurred three times an hour during the day (0800-2200 hours) and once an hour during the night (2200-0800 hours). The hours defining the "day" and "night" were based upon the literature (Bystritsky, Craske, Maidenberg, et al., 1995), and were adopted so as to minimize the possible interference of subjects' sleep patterns by BP cuff inflations.

Hemodynamic indices derived from ambulatory blood pressure monitoring (ABPM) included systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP), and pulse rate (a.k.a., HR). Because these parameters were assessed every 20 minutes during the day (when ischemia was most likely to occur) ischemia-related BP measurements were those occurring within 10 minutes of each ischemic episode. This standard has been used before in the research literature (Deedwania et al., 1990).

Activity monitoring. An accelerometer-based physical activity-monitoring device (Mini-Mitter Actiwatch[®], Mini-Mitter Inc.; Sunriver, Oregon), comparable in size and weight to an ordinary wristwatch, was placed on the wrist of patients' non-dominant arms. The actiwatch monitor uses an accelerometer to monitor the degree of gross

physical motions that occur beyond a .01 g threshold. The maximum sampling frequency of the actiwatch is 32 Hz.

The type of sensor used by these devices integrates the degree and speed of an individual's motions, and records changes in the magnitude of the sensor's electrical current. An increased degree of speed and motion will produce an increase in voltage that, in turn, will be stored by the unit as a higher number of "activity counts" per user-defined assessment epoch. For this study, activity data was collected every minute and was synchronized to both the ambulatory ECG and BP monitors. The use of these types of devices to reliably measure physical activity has been extensively validated against observational, self-report, and VO₂ max. criteria (Patterson, Krantz, Montgomery, et al., 1993).

Structured Diary System. Volunteers were asked to complete a validated and previously published structured diary system (Hedges et al., 1990) in which subjects' were asked to report their physical and mental activities and moods throughout the day (see Appendix 3). Participants were asked to complete a diary entry every time a BP cuff inflation occurred during wakeful hours (~ 2-3 entries/hour, for a maximum of ~ 42 daily entries). This strategy provided essential qualitative information regarding patients' physical and emotional states that corresponded to simultaneous quantitative measurements of activity, HR, and BP. Previous studies have shown that physical activity measures obtained by this structured diary were significantly correlated with 24-hour physical activity levels, as measured by automated activity monitors (Patterson et al., 1993).

Power Analysis. The sample size for this study was derived using a 5% Type I error rate and 80% estimated power. The ability to detect a significant HRV difference between CAD patients was estimated using the findings of Bigger and colleagues (Bigger et al., 1995). Since there was no comparable information available regarding HRV of ischemic CAD patients, this index was approximated by lowering Bigger et al's. HRV estimates for CAD patients by 10%. That said, it was estimated that a total of sixty-one volunteers were required to detect a significant group difference in 24-hour HRV (SDNN). Therefore, the 55 CAD patients who were recruited for this study should have provided adequate power for all statistical comparisons. This power analysis was calculated by using nQuery Advisor 3.0 for Windows (Elashoff, Dixon, Crede, & Fotheringham, 1995).

Statistical Analyses. The first hypothesis regarding differences in 24-hour HR, BP, and number of daily life ischemic episodes was tested using univariate analysis of variance (ANOVA). The two independent variables were the classification of CAD patients (i.e., low/high SDNN, low/high RMSSD) and the three dependent variables were 24-hour HR and BP levels, and the number of recorded ischemic episodes. There was no Type I correction for multiple comparisons due to the exploratory nature of this hypothesis.

Related to the first hypothesis was the predicted difference in 24-hour SDNN, RMSSD, HR, and BP among CAD patients with and without ischemia. This hypothesis was tested using univariate ANOVA. Four separate ANOVAs were performed, one for

each dependent variable (i.e., 24-SDNN, RMSSD, HR, BP). The independent variable for each comparison was group membership (i.e., ischemic CAD, non-ischemic CAD).

The second hypothesis regarding group differences in HRV, HR, and BP during periods of matched low and high non-ischemic activity were tested using Student t-tests. The independent variable for each comparison was group membership (i.e., ischemic CAD, non-ischemic CAD) while the dependent variables were HR, BP, and HRV indices measured during low and high activity.

Related to the second hypothesis was the predicted group difference in the change in HRV, HR, and BP from low to high periods of exertion for CAD patients with and without ischemia. Subtracting “low” activity measurements of HRV, HR, and BP from “high” activity measurements was used to create these change scores. Student t-tests were then used to assess whether or not there were group differences in HR, BP and HRV change scores.

The third hypothesis regarding activity-related changes in HRV, HR, and BP prior to the onset of ischemia was tested using repeated measures ANOVA. Ambulatory physical activity, HRV, HR, and BP data corresponding to the 30 minutes before each episode of ischemia were analyzed as within-subject factors. The mean level of these variables (as measured at the onset of ischemia) was compared with those measured over the 30-minute period preceding the onset of ischemia by using simple contrast tests.

RESULTS

Results are presented in the following order: First, patient characteristics are presented (i.e., sociodemographic data, clinical status, medications) followed by

descriptive information regarding ambulatory myocardial ischemia, physical activity, blood pressure, heart rate, and heart rate variability. This section also includes analyses regarding the validation of the methods used to measure the aforementioned study variables. Subsequently, the study hypotheses are addressed in order.

Patient Characteristics

Demographics. Of the 55 subjects enrolled in this study, 2 voluntarily withdrew from the study and their data are not included in these analyses. The remaining 53 subjects (44 men, 83.0%) had a mean age of 65.4 ± 7.6 years (range= 45-80 years). Forty-eight subjects (90.6%) were Caucasian, 4 were African American (7.5%), and 1 was Asian American (1.9%). Mean years of education were 15.9 ± 2.6 years (range = 9-21 years).

Clinical Status. Of the 53 patients, 46 (86.8%) had angiographically documented CAD. Of the 7 remaining patients without angiograms, 4 (7.5%) had a previous myocardial infarction while 3 (5.7%) had a positive exercise stress test and a high probability of CAD ($\geq 80.0\%$) according to Bayesian analysis of risk factors and symptoms (Rozanski, Diamond, Forrester, et al., 1984). Of the 46 patients with prior angiograms, 21 (45.7%) had single-vessel disease, 12 (26.1%) had two-vessel disease, 10 (21.7%) had three-vessel disease, and 3 (6.5%) lacked clinical information regarding the number of diseased vessels. Most patients ($n = 47$, 88.7%) had New York Heart Association Class I anginal symptoms, 5 patients (9.4%) had Class II symptoms, and 1

patient (1.9%) had Class III symptoms. Twenty-nine patients (54.7%) had a history of hypertension and 45 (84.9%) had elevated total cholesterol levels.

All patients remained on medications during their participation in this study. Among the 53 patients, 33 (62.3%) were prescribed beta-adrenergic blockers, 16 (30.2%) calcium-channel blockers, 18 (34.0%) vasodilators, 22 (41.5%) ACE-inhibitors, 47 (88.7%) lipid-lowering drugs, and 47 (88.7%) aspirin.

Ambulatory ECG analyses. A total of 2309.7 ± 8.2 hours of ambulatory ECG (Holter) data was recorded from this sample. Six patients (11.3%) were limited to 24-hours of Holter data due to technically deficient recordings as determined by the ECG core laboratory at Brigham and Women's Hospital (Boston, Massachusetts). There was an average of 1.8 ± 0.34 days of ECG data recorded for each patient.

Of the 53 patients, 9 (8 men) experienced a total of 18 episodes of ischemia (2.0 ± 1.3 episodes/patient) (see Table 1 for group demographic information). The average duration of each episode of ischemia was 23 ± 21 minutes (range= 1.25-69.0 minutes) for a total of 420.5 minutes of recorded ischemic time. Table 2 provides further information regarding these events. As is evident in Table 2, there was a clear bimodal distribution to the duration of ischemic events recorded in this study. Morning episodes (i.e., < 12 pm) averaged 17 ± 20 minutes in duration, afternoon episodes (i.e., 12 pm - 6 pm) averaged 45 ± 27 minutes, and evening episodes (> 6 pm) averaged 23 ± 17 minutes. Figure 1 illustrates the diurnal distribution of these events. There were nine episodes of morning ischemia (50.0%), 3 episodes (16.7%) of afternoon ischemia, and 6 episodes (33.3%) of evening ischemia. No ischemic episodes occurred at night in this sample. All episodes of ischemia occurred between 0532 and 2203 hours. None of the 18 episodes of ischemia

were associated with reports of chest pain. As illustrated in Table 1, there were no significant differences between ischemic and non-ischemic CAD patients in terms of their demographic information, clinical histories, or medication regimens. Only 4 patients were current users of tobacco products making group comparisons meaningless.

Additional ECG analyses were used to generate both time and frequency domain measurements of heart rate variability. There was an average of 1.8 ± 0.34 days of HRV data available for each patient. Mean 24-hour HRV (SDNN) was 146 ± 34.3 ms. (range = 76 to 220 ms.) while mean 24-hour vagal tone (RMSSD) was 87 ± 41 ms. (range = 28 to 185 ms.). Mean LF power was 7.25 ± 0.84 ms² (log normalized; range = 5.03 to 9.05 ms²) while mean HF power was 6.50 ± 0.81 ms² (log normalized; range = 4.72 to 8.53 ms²). The mean ratio of these two, LF/HF, a rough index of sympathovagal tone, was 1.12 ± 0.06 ms² (log normalized; range = 0.98 to 1.24 ms²).

Ambulatory Physical Activity, Blood Pressure, and Heart Rate Monitoring.

Physical Activity. Automated physical activity data for 4 subjects was not available for analysis. Two patients' data was technically deficient due to noise and two patients' data was lost after download of their monitors. A total of 2356.6 ± 1.0 hours of concomitant physical activity, blood pressure, and HR data was recorded from the remaining 49 subjects. There was an average of 2.0 ± 0.04 days of physical activity data recorded for each patient. Figure 2 illustrates the diurnal distribution of mean physical activity levels for this sample.

Ambulatory Blood Pressure and Heart Rate. There were 4611 measurements of ambulatory blood pressure and heart rate recorded from this sample, or an average of 94 ± 12 measurements per patient (range = 47-111 recordings). On an hourly basis, this translated into 2.5 ± 0.35 recordings/hour during wakeful hours, 0.91 ± 0.11 recordings/hour during sleep, and 1.96 ± 0.25 recordings/hour overall. As shown in Table 3, the mean SBP for the group was 124 ± 11 mm Hg, the mean DBP was 71 ± 7 mm Hg, and the mean HR was 66 ± 9 bpm. Figures 3 and 4 illustrate the diurnal distribution of mean hourly blood pressure and HR levels with respect to mean physical activity levels. The hourly data in these figures was used to correlate mean hourly physical activity levels with mean hourly HR and mean hourly BP levels for the entire sample. Aggregate correlations of all subjects 24-hour SBP, DBP, and HR with ambulatory physical activity levels were high $r_{(24)} = 0.90$, $p < .001$; $r_{(24)} = 0.93$, $p < .001$; $r_{(24)} = 0.78$, $p < .001$, respectively. In contrast, when calculated on a per patient basis (i.e., not aggregated per patient, per hour), the correlations among these variables were more variable in magnitude (see Table 4). Regardless, the majority of these intra-subject correlations of physical activity with SBP, DBP, and HR were statistically significant (71.4%, 67.3%, and 83.7% significant correlations, respectively).

Structured Diary. There were a total of 3754 diary entries recorded by 48 of the 49 subjects with physical activity data. One patient did not adequately complete his diary. There was an average of 78 ± 18 diary entries recorded per patient during their participation (range = 23 - 99 entries) with an average of 39 ± 10 diary entries recorded per study day. There were 3639 diary entry ratings of physical effort and 3631 diary entry ratings of mental effort. These diary ratings were highly skewed towards lower values.

Mean sample ratings for physical and mental effort were 1.5 ± 0.76 and 1.8 ± 0.85 , respectively (answer range= 1 ‘not at all’ to 5 ‘very much’). There were 3484 diary entry ratings of physical effort and 3476 diary entry ratings of mental effort that had corresponding measurements of ambulatory physical activity levels. Because self-ratings of effort were skewed, in order to correlate self-reported physical and mental effort with ambulatory physical activity levels, Spearman rank-order correlations were used. The correlation between self-reported physical effort and ambulatory physical activity levels was weak but significant, $r_{(3484)} = 0.32$, $p < .001$. The correlation between self-reported mental effort and ambulatory physical activity levels was even weaker but still significant, $r_{(3476)} = 0.10$, $p < .001$. The mean ambulatory physical activity level for each level of physical and mental effort rating (i.e., 1-5) was calculated. Figure 5 graphically illustrates the mean ambulatory physical activity level corresponding to each level of patients’ self-reported physical and mental effort. Univariate analysis of variance revealed that there was a significant relationship between patients’ self reported ratings of physical effort (i.e., 1-5) and mean ambulatory physical activity levels, $F_{(4,3479)} = 110.19$, $p < .001$, such that patients’ mean ambulatory physical activity levels increased sequentially with higher self-ratings of physical effort. Specifically, Tukey post hoc analyses revealed a significant increase in patients’ mean ambulatory physical activity levels corresponding with self-reported ratings of “1 - not at all” versus “2” (130.11 ± 188.37 counts vs. 221.58 ± 245.14 counts, $p < .001$) as well as from ratings of “2” to “3” (221.58 ± 245.14 counts vs. 380.14 ± 394.37 counts, $p < .001$). However, there was no significant difference in ambulatory physical activity levels corresponding to higher self-ratings of physical effort (i.e., 3-5), despite an increasing trend in mean activity levels.

Mean physical activity levels corresponding to physical effort self-ratings of “3” (380.14 ± 394.37 counts), “4” (428.41 ± 389.02 counts), and “5 – very much” (580.64 ± 638.76 counts) were statistically similar (p 's $> .05$). There was considerable inter-subject variability among the correlations of self-reported physical and mental effort with ambulatory physical activity levels. The mean correlation of ambulatory physical activity levels with self-reported physical effort for this sample was 0.32 ± 0.22 (correlation range = -0.16 to 0.72). Of these 48 correlations, 30 (62.5%) were statistically significant ($p < .05$), with the weakest significant correlation being $r = 0.21$, $p = .049$. The mean correlation of ambulatory physical activity levels with self-reported mental effort for this sample was 0.03 ± 0.16 (correlation range = -0.32 to 0.42). Of these 48 correlations, 10 (20.8%) were statistically significant ($p < .05$), with the lowest significant correlation being $r = -0.25$, $p = .05$.

Hypothesis 1: Reduced Heart Rate Variability as a Predictor of Higher 24-Hour Heart Rate and Blood Pressure Levels and Ischemic Burden.

As outlined in the Hypothesis 1, patients with lower 24-hour HRV (SDNN) and vagal tone (RMSSD) were predicted to have significantly higher levels of 24-hour HR and BP, as well as more episodes of ambulatory ischemia when compared to patients with more preserved levels of cardiac autonomic tone. To test this hypothesis, median values of heart rate variability (SDNN median = 147 ms.) and vagal tone (RMSSD median = 73 ms.) were used to categorize CAD patients into groups of “low” and “high” tone. To validate this method of classifying patients, “low” and “high” SDNN was cross-

tabulated with “low” and “high” RMSSD. This strategy was successful considering that 73.1% (19/26 patients) classified as “low” SDNN were likewise classified as “low” RMSSD, whereas 74.1% (20/27 patients) classified as “high” SDNN were likewise classified as “high” RMSSD, $X^2 = 11.8$, $n=53$; $p < .005$.

As illustrated in Figure 6, univariate analysis of variance revealed that CAD patients with lower SDNN ($n=26$) had significantly higher 24-hour HR levels (70 ± 7 bpm) than did patients with higher SDNN (65 ± 9 bpm; $n = 27$), $F_{(1,51)} = 4.67$, $p < .05$. Similarly, CAD patients with lower RMSSD ($n = 26$) had significantly higher 24-hour HR levels (70 ± 8 bpm) than did patients with higher RMSSD (65 ± 8 bpm; $n = 27$), $F_{(1,51)} = 4.40$, $p < .05$. However, contrary to Hypothesis 1, univariate analysis of variance revealed no significant differences with regard to patients’ 24-hour blood pressure levels (p ’s $> .05$) or the number of episodes of ischemia they experienced ($p > .05$) (see Table 5 for further information regarding these data).

Further analyses examined whether or not patients experiencing ambulatory ischemia ($n = 9$, 17.0%) had significantly lower levels of cardiac autonomic tone than non-ischemic CAD patients ($n = 44$, 83.0%), as evidenced by higher levels of 24-hour HR and BP. Contrary to expectations, however, patients with ST-segment depression had significantly higher 24-hour SDNN than did non-ischemic patients (172.5 ± 25.5 ms. vs. 141.0 ± 33.9 ms., respectively), $F_{(1,51)} = 7.15$, $p < .05$, as well as significantly lower levels of 24-hour HR compared to non-ischemic patients (63 ± 8 bpm vs. 69 ± 9 bpm, respectively), $F_{(1,51)} = 4.12$, $p < .05$. Figure 7 illustrates these findings. Moreover, these findings were unchanged when considering only those patients with uncomplicated CAD (i.e., no previous MI). Compared to non-ischemic patients ($n = 21$), patient with ischemia

($n = 7$) had significantly higher 24-hour SDNN (171.2 ± 16.3 ms.) than did non-ischemic patients (135.9 ± 26.3 ms.), $t_{(26)}=3.32$, $p < .005$, as well as a trend towards lower 24-hour HR levels (64 ± 8 bpm) when compared to non-ischemic patients (69 ± 9 bpm), $t_{(26)}=1.29$, $p = 0.20$.

The above results could not be explained by the disproportional use of beta-adrenergic blocking agents by patients with ischemia (see Table 1). For patients with ischemia, 66.7% ($n = 6$) were currently taking beta-blockers compared to 61.4% ($n = 27$) of the non-ischemic sample. As well, both groups were prescribed a median dosage of 50 mg. of beta-blockers per day. *Post hoc* analyses revealed no significant difference in beta-blocker use between patients with and without ST-segment depression, $X^2 = 0.08$, $p = \text{NS}$, or between their mean daily dose of beta-blockers $t_{(31)} = 0.49$, $p = \text{NS}$.

On the other hand, further analyses revealed that the majority of non-ischemic patients had previously experienced a myocardial infarction ($n = 22$, 51.2%) compared to less than one-quarter of the ischemic patients ($n=2$, 22.2%, $p = \text{NS}$). While not statistically significant, this disparity suggests the possibility that more non-ischemic patients had pre-existing myocardial injury than did the ischemic group. However, subgroup analysis of available ejection fraction data revealed that non-ischemic patients ($n = 17$) did not differ from ischemic patients ($n = 3$) in terms of EF ($57 \pm 10\%$ vs. $53 \pm 8\%$, respectively), $t_{(18)} = 0.61$, $p = 0.6$. Moreover, analyses also revealed that ischemic and non-ischemic patients were similar in terms of previous revascularization attempts, with 43.2% ($n = 19$) of non-ischemic patients and 55.6% ($n = 5$) of ischemic patients having received some degree of revascularization via angioplasty and/or stent placement ($X^2 = 0.46$, $p = 0.50$; $n = 53$). Thus, while the incidence of MI was higher in the non-ischemic

sample, and may still account for the paradoxical findings regarding HRV and HR in these patients, the relevance of this finding is unclear given the comparability of ischemic and non-ischemic patients on EF and previous reperfusion procedures. Finally, contrary to predictions, there were no significant group differences found in 24-hour RMSSD or blood pressure levels between patients with and without ST-segment depression (p 's > .05), irrespective of whether or not patients had previously experienced an MI (p 's > .05) (see Table 6 for further information regarding these data).

Hypothesis 2: Group Differences in Heart Rate Variability, Heart Rate, and Blood Pressure for Patients with and without ST-Segment Depression During Non-ischemic Periods of “Low” and “High” Physical Activity.

Whereas the first set of hypotheses tested for group differences in 24-hour measures of HRV, HR, and BP, Hypothesis 2 tested for group differences in autonomic and hemodynamic tone when ischemic and non-ischemic CAD patients were engaged in discrete periods of both “low” physical activity and “high” physical activity. It was predicted that ischemic CAD patients would have significantly lower levels of cardiac vagal tone (HF), significantly higher sympathovagal balance (indicative of reduced vagal tone), and significantly higher levels of HR and BP when compared to non-ischemic CAD patients, irrespective of physical exertion levels.

To test Hypothesis 2, 30-minute epochs of sustained “low” and “high” physical activity data were selected for each patient during periods of non-ischemic activity. “Low” and “high” physical activity were defined for each patient by use of their lower

and upper quartiles of physical activity data (i.e., $\leq 25\%$ and $\geq 75\%$ activity distribution). In order to avoid the possible influence of circadian rhythms on the findings, all selected epochs were from the afternoon hours (except for one patient whose data required the use of morning physical activity data). Again, the chosen epochs for these analyses included no evidence of ambulatory ischemia.

In order to validate that the chosen 30-minute epochs of “low” and “high” physical activity were equal for both groups of patients, t-tests were performed. The “low” activity level of ischemic patients was 25.3 ± 20.0 counts/minute compared to 22.1 ± 21.4 counts/minute for the non-ischemic group, $t_{(46)} = -0.41$, $p = \text{NS}$. The “high” activity level of ischemic patients was 501.2 ± 229.7 counts/minute compared to 449.1 ± 268.4 counts/minute for the non-ischemic group, $t_{(46)} = -0.54$, $p = \text{NS}$. In other words, “low” and “high” physical activity levels were equally matched between patients with and without ST-segment depression for the chosen epochs of non-ischemic activity. Figures 8 and 9 (left panels), illustrate these data. Figures 8 and 9 also reveal that patients with ischemia did not differ from non-ischemic patients in terms of their HRV, HR, or BP as was proposed. Contrary to prediction, ischemic CAD patients actually had a lower HR than non-ischemic patients during periods of lower physical activity ($p = .052$; see Figure 8). This finding is most likely a reflection of the lower overall HR level found for this group and not related to this particular period of “low” physical activity. Thus, it appears that the autonomic and hemodynamic response of CAD patients to discrete periods of low and high physical activity are similar, irrespective of whether or not some patients eventually experienced ambulatory ischemia (see Table 7 for the information regarding these analyses).

Hypothesis 2 further speculated on the relationship between physical activity, HRV, HR, and BP for patients with and without ischemia by proposing group differences in the change in autonomic and hemodynamic tone from “low” to “high” periods of physical activity. Specifically, it was predicted that the shift in cardiac vagal tone (HF), sympathovagal balance (LF/HF), HR, and BP from low to high periods of exertion would be greater for ischemic than non-ischemic CAD patients. To test this hypothesis, change scores were created for each parameter by subtracting “low” parameter values from “high” parameter values. As illustrated in Figure 10, despite some differences in data trends, there were no significant differences in HRV (p 's $> .05$), HR ($p = 0.74$), SBP ($p = 0.17$), or DBP ($p = 0.21$) change scores for patients with or without ST-segment depression.

Hypothesis 3: Changes in Physical Activity, Heart Rate, and Heart Rate Variability Prior to the Onset of Ambulatory Ischemia.

Hypothesis 3 predicted that, prior to the onset of ischemia, there would be a significant decrease in cardiac vagal tone (HF) and a significant increase in HR and sympathovagal tone (LF/HF) concurrent to pre-ischemic changes in physical activity. To test this hypothesis, data relating to the 30-minutes before each episode of ischemia ($n=18$) was analyzed. This time period was selected based upon the methodologies employed by previous studies investigating pre-ischemic changes in HRV (Brouwer et al., 1994; Goseki et al., 1994; Kop, Verdino, Gottdiener, et al., 2002; Vardas et al., 1996; Vardas et al., 1994). Figures 11-13 illustrate the changes in physical activity, HR, and

HRV that occurred during this time frame. (Blood pressure and self-reported physical and mental effort were dropped from these analyses because they were infrequently measured prior to the onset of ischemic events in these patients.).

As shown in Figure 11, there was a steep, significant rise in both physical activity, $F_{(2.3, 38.5)} = 4.65$, $p < .05$ and HR levels, $F_{(4.7, 79.7)} = 35.16$, $p < .001$ over the 30 minutes preceding the onset of ambulatory ischemia. Simple contrast tests revealed that the mean physical activity level at the onset of ischemia was significantly higher than all preceding time period assessments (p 's $< .05$), except for the measurement at 5 minutes prior to onset ($p = 0.43$; see Table 8 for means and standard deviations). Table 9 provides the results of these analyses. Simple contrast tests also revealed that the mean HR at the onset of ischemia was significantly higher than all preceding time period assessments (p 's $< .05$; see Table 8 for means and standard deviations and Table 9 for statistical results). As shown in Figure 11, physical activity and HR levels decreased immediately after the resolution of ambulatory ischemia.

Figure 12 illustrates the changes that occurred in HR and HRV, specifically HF and LF, over the 30 minutes before the onset of ischemia. Despite the significant increase in HR prior to ischemia (see above discussion), repeated measures ANOVA revealed no significant changes in LF or HF during this 30-minute period (p 's $> .05$; see Table 8 for means and standard deviations). Despite the lack of significant findings, the reduction in HRV before ischemia was in the predicted direction. Furthermore, these findings were unchanged when re-analyzed for patients with uncomplicated CAD (i.e., no previous MI). There were no significant changes in HF or LF during the 30-minute period preceding the onset of ischemia for patients without a history of myocardial infarction

(p 's $> .05$). However, additional analyses revealed a significant inverse relationship between 24-hour vagal tone (RMSSD) and ischemic duration, Spearman $r = -0.60$, $p < .01$, $n=18$, suggesting that episodes of ischemia lasted longer in patients with lower levels of vagal tone. This relationship was not found when considering pre-ischemic spectral components of vagal tone (HF).

On the other hand, as shown in Figure 13, there was a brief increase in sympathovagal tone (LF/HF) beginning 10 minutes before the onset of ischemia, $F_{(2,34)} = 2.82$, $p = .07$. At 5 minutes before ischemia, the apex in LF/HF ($1.30 \pm 0.36 \text{ ms}^2$) was significantly higher than the level coinciding with the onset of ischemia ($1.13 \pm 0.23 \text{ ms}^2$), $F_{(1,17)} = 5.19$, $p < .05$, indicating that an acute pre-ischemic shift in autonomic tone had occurred. This same spike in sympathovagal tone was also evident when the data were re-analyzed for just those patients with uncomplicated CAD, $t_{(15)} = 3.50$, $p < .005$. Further analysis of Figure 11 revealed that the timing of the shift in sympathovagal tone coincided with the peak in pre-ischemic physical activity and HR levels before the onset of ischemia. What is more, during this period of heightened activity (i.e., 5 minutes before ischemia) there was a significant positive relationship between LF and ischemic duration, Spearman $r = 0.50$, $p < .05$, suggesting that episodes of ischemia lasted longer when immediately preceded by higher levels of sympathetic tone. Collectively, these findings suggest that the onset of ischemia occurred: 1) when both physical activity and HR levels were peaking; 2) during a period of heightened sympathovagal tone (LF/HF), and; where of longer duration: 1) in patients with lower levels of 24-hour vagal tone (RMSSD), and; 2) when immediately preceded by higher levels of sympathetic tone (LF).

DISCUSSION

The autonomic nervous system regulates homeostatic control over resting heart rate and blood pressure levels, as well as the augmentation of heart rate and blood pressure in response to encountered challenges. In some patients with coronary artery disease (CAD), however, autonomic-cardiac regulation can be altered as a result of myocardial injury and coronary disease. This study was designed to examine whether changes in autonomic-cardiac regulation: (1) are associated with altered hemodynamic regulation in CAD patients; (2) identify CAD patients at-risk for ambulatory ischemia; and (3) are related to changes in physical exertion and heart rate before the onset of ambulatory myocardial ischemia. The following sections discuss the study findings in light of the current literature.

Reduced Heart Rate Variability as Related to Differences in Hemodynamic Tone and Ischemic Burden.

Hypothesis 1 was designed to address whether or not CAD patients with altered autonomic tone (i.e., reduced 24-hour heart rate variability: HRV) had higher 24-hour heart rate and blood pressure levels and more episodes of myocardial ischemia when compared to CAD patients with preserved levels of autonomic tone. Partial support for this hypothesis was found. Specifically, CAD patients with lower 24-hour HRV (SDNN) and vagal tone (RMSSD) were found to have significantly higher 24-hour heart rate levels when compared to patients with higher HRV values. However, no group

differences were found with regard to 24-hour blood pressure levels or the number of ischemic episodes patients experienced during monitoring.

The observed inverse relationship between 24-hour rate variability and mean 24-hour heart rate levels affirms the notion that autonomic tone elicits central effects on heart rate. Besides lower SDNN, lower vagal tone (RMSSD) was also related to higher heart rate levels. This finding is consistent with the physiologic mechanisms proposed for heart rate control (Guyton et al., 1996). For example, studies have shown that acute increases in heart rate occur as a result of a withdrawal in parasympathetic input to the heart (Fagraeus et al., 1976; Robinson et al., 1966). The current study confirmed that CAD patients with depressed measures of vagal tone had higher levels of 24-hour heart rate. However, it should be noted that this finding, while important, is not restricted to patients with coronary disease. In fact, the studies cited above regarding vagal tone and heart rate were actually conducted on healthy individuals. Thus, the fact that CAD patients with lower levels of autonomic tone also had higher levels of 24-hour heart rate should not be construed as a marker for altered autonomic-cardiac regulation in these patients.

Moreover, there was no evidence to suggest that reduced HRV was related to higher blood pressure levels in these patients. This finding may reflect the multiple sympathetic and parasympathetic determinants of blood pressure. Autonomic control over systemic blood pressure is very complex (Ralevic et al., 1993), and the present findings suggest that 24-hour heart rate variability and 24-hour blood pressure are determined by different exogenous and endogenous factors (e.g., circadian variation, short term changes in activity) (Kop, Krantz, & Baker, 2001). In addition, blood pressure

was sampled at set intervals of 3 times/hour during the day and 1 time/hour during the night (see Methods), whereas HRV and HR were monitored continuously, increasing the probability of the latter to reveal higher correlations. Further research is needed to analyze HRV and blood pressure at overlapping 5 to 30 minute time intervals.

Finally, the fact that reduced 24-hour HRV was not related to the number of ischemic episodes experienced by CAD patients was unexpected. Previous studies have shown that reduced HRV is a clear marker for adverse events, particularly death, in post-infarct patients with coronary disease. For example, Kleiger and colleagues (1987) found that patients with SDNN less than 50 ms. had a fourfold increased risk for death when compared to patients with SDNN greater than 100 ms. Patients with SDNN between 50-100 ms. were roughly one and a half times more likely to die than patients with SDNN greater than 100 ms. In the current study, however, there was no group difference in the number of ischemic events experienced by patients with lower or higher levels of HRV. Further review of the data, however, revealed that the cutoff values for defining “low” HRV and vagal tone in this sample (i.e., $SDNN \leq 147$ ms.; $RMSSD \leq 73$ ms.) were much higher than in the study by Kleiger and colleagues (1987). In other words, it appears that the current sample was comparatively “healthier” in terms of autonomic-cardiac tone, which may explain the lack of findings regarding ischemic burden. Then again, the fact that patients remained on their medications during their participation may have influenced both their autonomic tone as well as their ischemic burden. Previous reports have also demonstrated that day-to-day variability in ischemic burden was not associated with differences in 24-hour HRV, and that correlations between HRV across two

consecutive days are high (range 0.87 to 0.98) despite substantial fluctuations in ischemic burden across the same 2-day period (Pardo, Merz, Paul-Labrador, et al., 1996).

Collectively, the above findings do not support a relationship between compromised autonomic-cardiac regulation and an increased risk for experiencing ambulatory myocardial ischemia in patients with coronary artery disease and suggest that the increased risk of cardiovascular mortality associated with reduced HRV indices may be related to ANS-mediated arrhythmic vulnerability rather than ischemic burden.

Differences in Autonomic and Hemodynamic Parameters Between CAD Patients with and without Evidence of Ambulatory Myocardial Ischemia.

While the first hypothesis examined whether or not individual differences in HRV were related to differences in hemodynamic tone and ischemic burden in CAD patients, additional analyses examined this association from a different perspective, predicting that ischemic CAD patients would have significantly lower 24-hour HRV markers as well as significantly higher 24-hour heart rate and blood pressure levels when compared to non-ischemic patients. Contrary to expectations, however, the opposite relationships were found. Patients with evidence of ambulatory ischemia were actually found to have significantly higher levels of 24-hour SDNN and significantly lower levels of 24-hour heart rate when compared to non-ischemic patients. There were no group differences found with regard to 24-hour markers of vagal tone or blood pressure levels. These relationships persisted when considering only those patients with uncomplicated CAD.

Because these findings were both unexpected and opposite to expectations, *post hoc* analyses were performed in an attempt to explain why ischemic CAD patients had lower 24-hour heart rates and higher SDNN when compared to non-ischemic patients. The first analysis examined the possibility that the differential use of cardiovascular medications, specifically beta-blocking agents, was responsible for these results. Beta-blocking agents are widely prescribed medications because of their central effect of lowering heart rate. Studies have also shown that beta-blockers alter autonomic-cardiac regulation, presumably through increasing vagal tone (Burger & Kamalesh, 1999; Lampert, Ickovics, Viscoli, et al., 2003). In the current study, however, no differential use of beta-blocking agents or their prescribed daily dosages was found between CAD patients with and without ischemia. This finding was further validated by the fact that no group differences were found with regard to 24-hour vagal tone in this study.

Another possible explanation for these results is the existence of pre-existing myocardial injury. Myocardial injury – primarily from infarct – is believed to be a root cause for reduced autonomic-cardiac regulation in some CAD patients (Ahonen et al., 1975) as well as the primary risk factor associated with poorer outcomes in these patients (Bigger et al., 1992; Kleiger et al., 1987). Myocardial infarction results in reduced and sometimes complete absence of nerve fiber function in the zone of necrotic cardiac tissue, impairing autonomic regulation of the heart (Ahonen et al., 1975). Therefore, the second *post hoc* analysis examined whether or not there were group differences in patients' clinical histories regarding the presence of a previous myocardial infarction. Interestingly, less than 25% of the ischemic group had a history of MI whereas more than 50.0% of the non-ischemic group had a history of MI. Although this finding was not

statistically significant, it does show that more patients in the non-ischemic sample had pre-existing myocardial injury, possibly accounting for the incongruent findings of lower SDNN and higher heart rates in this group.

However, the above findings are tempered by the fact that both ischemic and non-ischemic patients were found to have preserved ejection fractions. Because ejection fraction is considered to be a standard clinical marker for myocardial pump function, this finding does not support the notion that previous damage from myocardial infarct was responsible for the paradoxical findings regarding heart rate variability and heart rate. Moreover, similar proportions of ischemic and non-ischemic patients were found to have undergone reperfusion procedures related to their coronary disease. Thus, even though more non-ischemic patients had a history of myocardial infarction than the ischemic group, the fact that both groups received similar treatment for their CAD again undermines the notion that previous myocardial damage was responsible for the observed differences in 24-hour autonomic tone and heart rate levels.

Collectively, the findings from the first set of hypotheses do not support a relationship between reduced autonomic tone and an increased risk for experiencing myocardial ischemia in patients with coronary artery disease. Moreover, the paradoxical finding of higher levels of autonomic tone in ischemic CAD patients persisted despite *post hoc* attempts to explain these findings in light of patients' medications, ejection fraction, and previous reperfusions. While previous studies have observed lower levels of autonomic tone in patients with coronary disease, particularly inducible vagal tone (Airaksinen et al., 1987), other studies have not. For example, Pai and colleagues (1995) failed to find differences in 24-hour HRV when comparing patients with uncomplicated

CAD to healthy controls. Specifically this study found that both 24-hour as well as spectral components of HRV were similar between patients with significant CAD, CAD patients with minimal disease, and healthy controls (Pai et al., 1995). Huikuri et al. (1994) also failed to find differences in 24-hour HRV when comparing CAD patients and healthy controls. However, of particular interest are the findings of Pardo et al. (1996), who demonstrated that day-to-day variability in ischemic burden was not associated with differences in 24-hour measures of HRV. Stated differently, this study showed that 24-hour measures of HRV were relatively insensitive to significant differences in ischemic burden, leading to the conclusion that such measures may be too global to reflect short-term changes in autonomic tone related to transient episodes of myocardial ischemia.

Comparing the Autonomic-Hemodynamic Stress Response of CAD Patients with and without Ischemia during Prescribed Periods of “Low and “High” Non-Ischemic Physical Exertion

The second set of hypotheses compared the autonomic-hemodynamic stress response of ischemic and non-ischemic CAD patients as measured during periods of matched “low” and “high” physical exertion. Hypothetically, if ischemic CAD patients have a diathesis for compromised autonomic-hemodynamic tone as was postulated, then such aberrations should be apparent even during periods of non-ischemic activity. Moreover, changes in physical activity should exacerbate these aberrations given the effect of physical activity on autonomic and hemodynamic regulation (Fagraeus et al., 1976; Robinson et al., 1966). However, there was no support found for these hypotheses.

Despite successful group matching on “low” and “high” physical exertion levels, ischemic CAD patients did not differ in terms of their heart rate variability, heart rate, or blood pressure response when compared to non-ischemic patients, irrespective of physical exertion levels. Moreover, there were no group differences found when comparing the change in heart rate variability, heart rate, and blood pressure levels from low to high periods of exertion. These results are important because they belie the assumption that pervasive aberrations in autonomic-hemodynamic tone increase the risk for ambulatory ischemia – a central tenet of the current study. Instead, findings for the first two sets of hypotheses suggest that autonomic-hemodynamic regulation and its alteration during periods of stress (i.e., exertion) are similar between CAD patients with and without evidence of ambulatory ischemia.

Changes in Physical Activity, Heart Rate, and HRV before the Onset of Ambulatory Myocardial Ischemia

Hypothesis 3 examined the relationships among physical activity, heart rate, and heart rate variability as related to the onset of ambulatory myocardial ischemia. It was predicted that there would be a significant pre-ischemic decrease in cardiac vagal tone (HF) and significant increase in sympathovagal tone (LF/HF) and heart rate concurrent to pre-ischemic changes in physical activity. Based upon the literature, relevant data from the half-hour period preceding the onset of ischemia was analyzed (Brouwer et al., 1994; Goseki et al., 1994; Kop et al., 2002; Vardas et al., 1996; Vardas et al., 1994). Findings from this study revealed that a significant rise in both physical exertion and heart rate

levels occurred over the half-hour preceding the onset of ambulatory ischemia. These pre-ischemic changes in activity and heart rate peaked with the onset of ST-segment depression, which is consistent with the findings of previous studies (Quigley, 2000). The occurrence of ischemia during periods of elevated activity and cardiac demand levels is also consistent with the findings of other studies examining cardiac demand-based models for myocardial ischemia (Barry et al., 1991; Deedwania et al., 1990; Krantz et al., 1996a; Parker et al., 1994). For example, in a study by Deedwania et al. (1990), pre-ischemic increases in heart rate (≥ 5 bpm) and systolic blood pressure (≥ 10 mm Hg.) occurred immediately before the onset of most episodes of ambulatory ischemia observed in their study, implicating increased cardiac demand as the trigger of these events. Krantz et al. (1996) reported findings similar to Deedwania and colleagues (1990) but in addition highlighted the potency of heightened levels of physical and mental activity as triggers of daily life ischemia. Moreover, both of these studies provided evidence for a circadian distribution to the occurrence of daily life ischemia, with a morning peak in events observed concurrent to the early morning changes in physical activity and cardiac demand that coincide with awakening. While the current study did not specifically examine the circadian onset of daily life ischemia, 50.0% of the ischemic events observed in this study occurred before noon, consistent with the findings of these previous studies (see Figure 1). Thus, the findings of the current study suggest that heightened levels of physical exertion and cardiac demand are complicit with the onset of ambulatory ischemia and suggest that changes in these variables may also contribute to the diurnal pattern of these events.

The current study findings were less clear, however, regarding the changes that occurred in autonomic tone before the onset of ischemia. Several studies have reliably demonstrated a significant withdrawal in vagal tone over the half-hour before the onset of ischemia (Brouwer et al., 1994; Goseki et al., 1994; Kop et al., 2002; Vardas et al., 1996; Vardas et al., 1994), concurrent to a significant increase in sympathovagal balance. In the current study, the trended changes in autonomic tone that occurred over this period were consistent with previous study findings but were not statistically significant, possibly as a result of underpowered analyses. Moreover, these findings did not change when considering only those subjects with uncomplicated CAD. Regardless, these trends corroborate the fact that a concomitant shift in autonomic tone does appear to occur with pre-ischemic changes in physical exertion and heart rate over the half hour preceding the onset of ischemia.

More importantly perhaps, was the additional finding of a brief significant rise in sympathovagal tone (LF/HF) during the last 10 minutes before the onset of ischemia. This finding is important for three reasons. First, other studies have noted that significant changes in sympathovagal and vagal tone occur specifically during the 10-minute period before the onset of ischemia (Goseki et al., 1994; Vardas et al., 1994). Second, it appears that the rise in LF/HF during this 10-minute period corresponded to the beginning of the peak in physical activity and heart rate levels before the onset of ischemia. While the importance of this acute shift in tone is unclear, its immediacy to the peak in physical activity and heart rate, not to mention the induction of ischemia, implicates it as a possible “trigger” of ambulatory ischemia. Finally, during this brief period (i.e., 5 minutes before ischemia) there was a significant relationship found between ischemic

duration and autonomic tone (LF, RMSSD) such that ischemic episodes endured longer in patients with lower levels of 24-hour vagal tone, as well as when immediately preceded by higher levels of sympathetic tone. Collectively, these findings provide general support for the notion that increased levels of physical exertion, cardiac demand, as well as acute shifts in autonomic tone precede the onset of ambulatory ischemia. Moreover, these findings are consistent with the physiologic mechanisms underlying activity-related changes in autonomic and hemodynamic tone and are consistent with the findings of previous studies examining the roles of physical exertion, heart rate variability, and increased cardiac demand in the onset of ambulatory myocardial ischemia.

Study Limitations

Low Occurrence of Ambulatory Ischemia. One limitation of the current study was the relatively low occurrence of ambulatory ischemia in this sample of patients. Roughly 17.0% of this sample (9 of 53 patients) experienced episodes of ambulatory ischemia. By comparison, Deanfield et al. (1983) reported that roughly 30-40% of their sample experienced episodes of ambulatory ischemia during monitoring. The key difference between these percentages, however, lies in the fact that the Deanfield study based its percentages on the occurrence of ambulatory ischemia in patients who had recent evidence of inducible ischemia during laboratory-based exercise stress testing. The current study did not use a positive stress test criterion for patient inclusion into the study

or *a priori* power analyses and, as a result, may have overestimated the likelihood of ambulatory ischemia that should have been expected for this sample.

Another possible explanation for the low occurrence of ambulatory ischemia in this study was the fact that all patients remained on their medications during their participation. As mentioned earlier, certain medications, such as beta-blockers, can help protect CAD patients from ischemia by lowering heart rates while also improving cardiac vagal tone (Burger et al., 1999; Lampert et al., 2003). Other medications, such as nitrates, can alleviate patient symptoms associated with the occurrence of ischemia. Thus, it is likely that maintaining patients' medication regimens during this study also contributed to the low occurrence of ischemia. The decision to keep patients on their medications was made to promote study feasibility and to avoid potential issues related to patient safety.

24-hour HRV and the Risk for Ambulatory Ischemia. A central postulate of the current study was that ischemic CAD patients would be identifiable by their proposed deficit in autonomic tone, as measured by heart rate variability. No support was found for this hypothesis however, and the validity of this model must be questioned. For example, other studies have failed to identify differences in 24-hour HRV indices when comparing CAD patients with healthy controls. For example, Pai and colleagues (1995) reported that 24-hour HRV indices were similar between patients with significant CAD, CAD patients with minimal disease, and healthy controls. Similarly, Huiruki and associates (1994) compared the 24-hour HRV of CAD patients to healthy controls and found no significant difference in any index of HRV. Huiruki et al. (1994) did find significant differences between CAD patients and controls in terms of their circadian regulation of autonomic tone, however, circadian regulation of autonomic tone was not examined in

the current study. Thus, the findings of this study as well as those of other studies have not been useful to risk-stratify CAD patients according to their 24-hour levels of heart rate variability.

In contrast, other studies have shown that lower levels of HRV are a clear risk factor for death in post-infarct CAD patients (Bigger et al., 1993; Bigger et al., 1992; Kleiger et al., 1987). However, there are two distinct differences between these studies and the current study. First, the cited studies purposely recruited CAD patients who were recently post-infarct. Such patients have considerably more abnormalities in autonomic-cardiac regulation as part of their recent myocardial damage. By comparison, the current study excluded CAD patients who had had an MI within 3 months of participation, an angioplasty within 6 months, or who had received a coronary stent within 1 year of participation. In addition, all patients with a history of coronary artery bypass surgery were excluded from the current study sample. Finally, all patients remained on their prescribed medications during their participation. In other words, the current sample was carefully screened according to its disease status and progression in order to exclude CAD patients with a greater proclivity for ischemia and altered autonomic nervous system activity based solely upon recent changes in their clinical histories. The second difference between this study and the studies cited above is sample size. For example, Bigger et al. (1992) examined the HRV of 715 CAD patients while Kleiger et al. (1987) examined the HRV of 808 CAD patients. For practical reasons, less than 60 CAD patients participated in the current study. Thus, it is possible that this study was underpowered in its attempt to identify differences in autonomic tone between CAD patients with and without ambulatory ischemia.

Ambulatory Blood Pressure Measurements. Another possible limitation of the current study was the nature of ambulatory blood pressure assessments, including the effect these measurements may have had on patients' behavior. Despite the sound scientific basis for measuring blood pressure changes in these patients, anecdotal reports from some patients suggest that this monitoring may have influenced their behavior patterns. Some patients reported halting their activities whenever their blood pressure cuff inflated while others reportedly limited their normal daily schedules because of the perceived interference of the blood pressure monitor. This finding is consistent with Kario et al. (1999), who reported that patients in their study were more likely to stop engaging in activities whenever ambulatory blood pressure cuff inflations occurred. In either instance, the effect of this change in behavior on the outcome of the current data is unclear. Furthermore, ambulatory blood pressure was only weakly correlated with patients' physical activity and heart rate levels (see Table 4). Again, this finding was consistent with other studies examining the relationships among ambulatory physical activity, heart rate, and blood pressure levels (Kario, 1999). For example, several studies have observed low correlations among ambulatory blood pressure, activity, and heart rate and conclude that the variability in these findings are due to the influence of exogenous factors such as mood, location, and posture on blood pressure levels (Kario, 1999; Schwartz, Warren, & Pickering, 1994; Shapiro & Goldstein, 1998). Finally, because the measurement of blood pressure in this study was relatively infrequent (i.e., every 20 minutes during the day and once per hour at night), blood pressure levels were excluded from some analyses because of insufficient data. Overall, the limitations related to

ambulatory blood pressure monitoring in the current study surpassed any contributions it made to the study findings.

Difficulties in Identifying Non-Ischemic Control Groups. Despite the noted limitations, this study successfully replicated previous findings regarding changes in physical activity and heart rate before the onset of ambulatory ischemia (Quigley, 2000). This study also corroborated the fact that pre-ischemic changes in autonomic tone appear to occur with pre-ischemic increases in physical exertion and cardiac demand levels. Still, the importance of these changes are not known considering that healthy individuals will show similar changes in autonomic tone and heart rate with increased levels of physical exertion (Fagraeus et al., 1976; Robinson et al., 1966). One way to address this issue would be to use a non-ischemic CAD control group for comparison. However, the difficulty in matching ischemic and non-ischemic CAD patients in terms of their daily life physical activity, heart rate, and autonomic tone levels hampered this study's ability to discern whether or not the pre-ischemic changes in these variables were implicit to the triggering of ischemic episodes, or rather simply circumstantial findings. Regardless, these findings were consistent with the findings of other studies examining cardiac-demand based models of ambulatory ischemia and highlight the importance of considering autonomic-cardiac regulation whenever investigating the occurrence of exertional ischemia.

Future Research

In the current study it was predicted that ischemic CAD patients would be identifiable from non-ischemic patients by a proposed deficit in autonomic tone, as measured by heart rate variability. Despite the lack of support for this proposal, future research investigating the relationship between autonomic-cardiac regulation and the risk for cardiac events may initially benefit from retrospective, exploratory analyses of large-scale ambulatory ECG databases. Such databases are common in both hospital as well as academic settings and could provide researchers with a large sample of previously analyzed recordings from which to base their conclusions regarding the utility of HRV in discriminating cardiac risk. Based upon these conclusions, researchers could then plan and execute well-powered prospective studies examining autonomic-cardiac regulation in cardiac patients. Such was the strategy of previous studies examining the risk for death in post-infarct CAD patients (Bigger et al., 1992; Kleiger et al., 1987)

In addition to ECG databases, clinical testing of patients' baroreceptor sensitivity could greatly improve research studies investigating the importance of vagal modulation in the occurrence of cardiovascular events. Tilt-table tests and carotid massage (i.e., Valsalva maneuver) are commonly used in the clinical evaluation of patients suspected of having vagally mediated cardiac events (i.e., syncope). In addition, these tests produce information regarding patients' levels of inducible vagal tone (e.g., vagal reserve), as well as information regarding patients' heart rate and blood pressure responses to alterations in vagal tone. The current study proposed that deficits in vagal tone would be related to changes in heart rate and blood pressure regulation, not to mention a risk factor for ambulatory ischemia in CAD patients. In retrospect, this study may have had better overall results if patients' baroreceptor sensitivity was assessed in conjunction with heart

rate variability, given the likelihood of improving the stratification of patients with lower vagal tone via the use of a multiple method strategy.

Clinical Implications

Heart rate variability has typically been considered to be a research tool and has not been widely adopted for use in the clinical evaluation of myocardial ischemia. However, recent trends have emerged for the clinical use of HRV assessments in the management of patients with cardiac arrhythmias. For example, two large manufacturers of implantable pacemakers and cardiac defibrillators have recently incorporated measures of heart rate variability within the clinical diagnostics of their devices. For example, Medtronic USA, Inc. (Minneapolis, Minnesota) has recently incorporated a 14-month trended measure of HRV (SDANN) in its latest family of pacemakers, defibrillators, and heart failure biventricular pacing devices. The Guidant Corporation (Minneapolis, Minnesota) has introduced a non-trended 24-hour measure of SDNN on its biventricular defibrillator. These measures of HRV are accompanied by daily measurements of patients' ambulatory physical activity levels (as measured by the accelerometer in these devices) as well as patients' daily heart rate trends.

In turn, the incorporation of HRV measures on widely used pacing and defibrillation systems means that cardiologists and electrophysiologists alike will begin to receive greater exposure to the usefulness of HRV in patient treatment. These data are presented in conjunction with more standard measures of patients' functional status, namely physical activity and heart rate. Monitoring concomitant changes in patients'

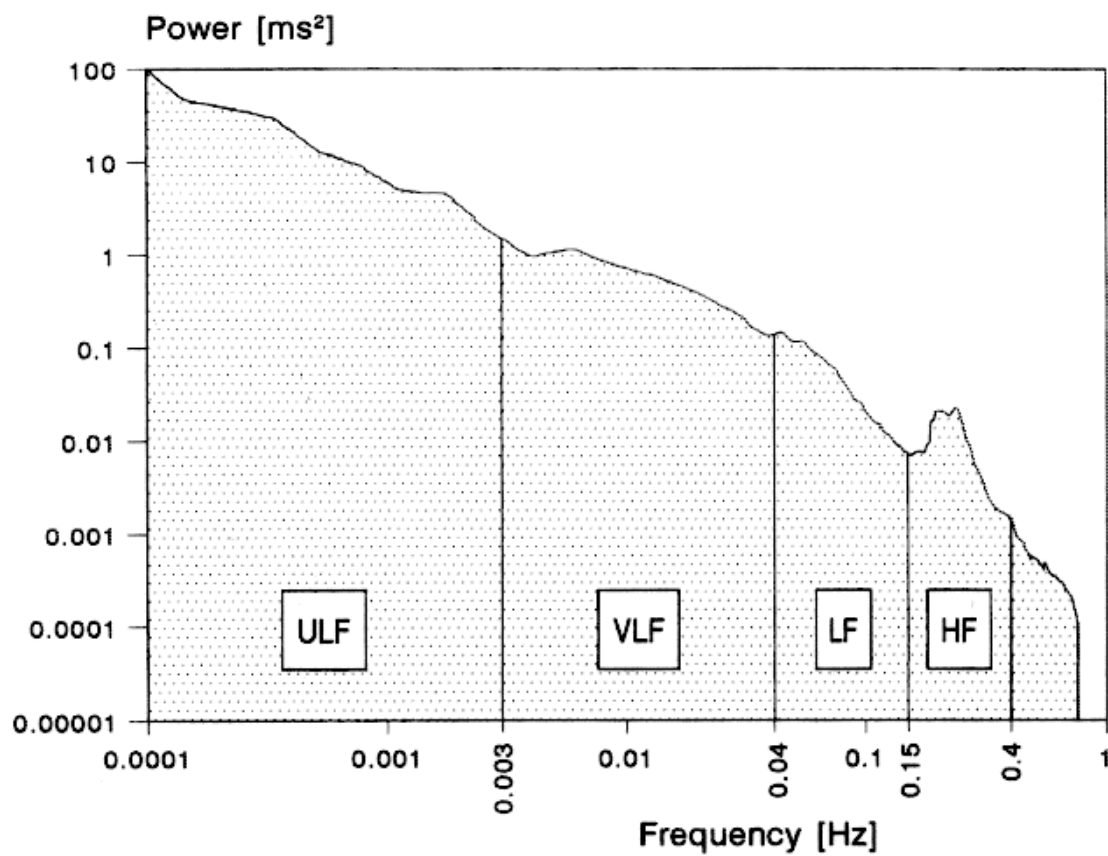
HRV, physical activity, and heart rate allows identification of possible changes in patients' conditions. For example, the worsening of patients' underlying heart failure or alternations in their conduction patterns as a result of supraventricular arrhythmias (i.e., atrial fibrillation and flutter) typically result in changes in autonomic tone, activity levels, and heart rate trends. Consequently, the decision by industry to include measures of HRV on its devices is likely to spur additional research into the clinical usefulness of this parameter in the treatment of patients with heart disease, and may ultimately modify the standard of care for these individuals.

Summary

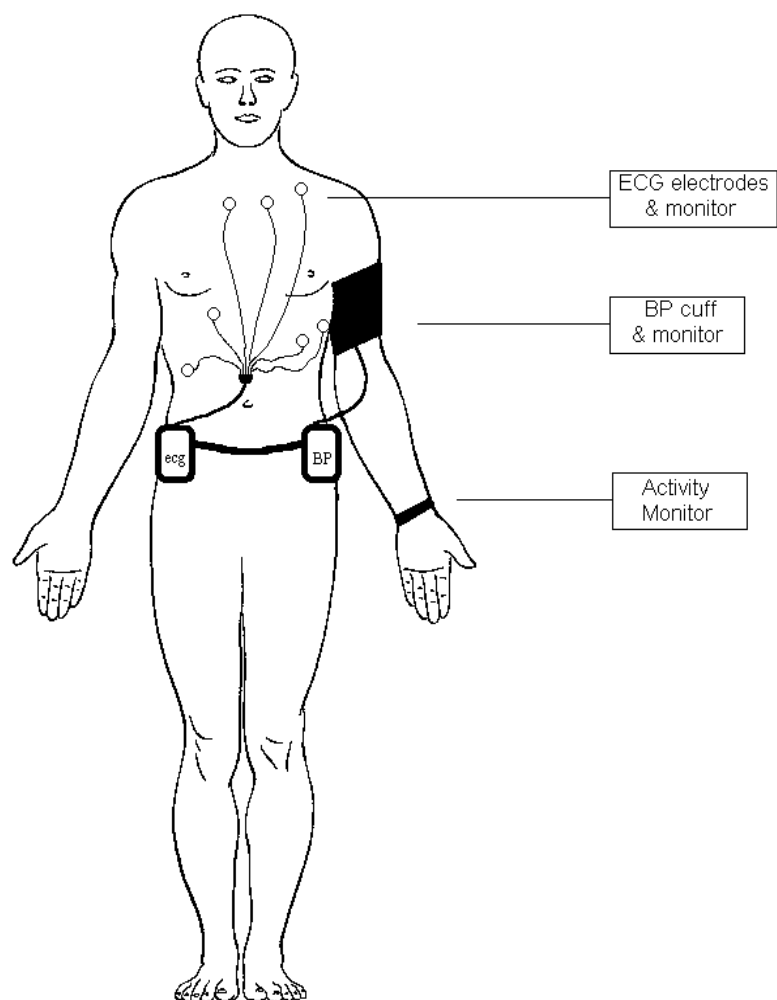
This study was designed to examine whether or not compromised autonomic-cardiac regulation in CAD patients: 1) was related to changes in 24-hour heart rate and blood pressure levels; 2) was useful in identifying CAD patients at risk for ambulatory ischemia or; 3) was related to pre-ischemic changes in physical exertion and heart rate with the onset of ambulatory ischemia. It was found that CAD patients with lower levels of 24-hour heart rate variability and vagal tone had significantly higher 24-hour heart rate levels than did CAD patients with more preserved levels of autonomic tone, but were similar with regard to their 24-hour blood pressure levels. More importantly, this study failed to show group differences in 24-hour measures of heart rate variability, heart rate, and blood pressure levels between CAD patients with and without evidence of ambulatory myocardial ischemia, and also failed to find differences in the hemodynamic stress responses of these groups to prescribed periods of "low" and "high" physical exertion, leading to the conclusion that measures of autonomic tone appear to lack utility

in stratifying CAD patients at risk for ambulatory ischemia. However, there was some evidence to suggest that alterations in autonomic tone coincide with increases in physical activity and heart rate levels prior to the occurrence of ambulatory ischemia, and that lower levels of 24-hour vagal tone predict longer episodes of myocardial ischemia, both of which highlight the importance of considering autonomic tone whenever discussing cardiac demand based models for ambulatory myocardial ischemia. In conclusion, the findings of this study reveal that global measures of autonomic tone do not discriminate CAD patients at risk for myocardial ischemia but support the situational importance of autonomic changes with the acute onset of ambulatory ischemia.

APPENDIX 1: Hypothetical Power Spectral Density Curve Estimated From a 24-hour ECG Recording (as adapted from Task Force, 1996, p.1047).



APPENDIX 2



APPENDIX 3

TIME ____: ____ AM/PM	ACTIVITY	AMOUNT OF EFFORT				
			Not at all			Very much
POSTURE:	going to sleep					
sit/stand/lying down	sleeping	physical	1	2	3	4 5
	rest	mental	1	2	3	4 5
LOCATION:	washing/dressing					
home/work/other	urinating/defecating					
	driving/passenger					
BEEPED? yes/no	shopping	frustrated	1	2	3	4 5
	eating/drinking	tense	1	2	3	4 5
Since last entry, have you had any...	house activity	sad	1	2	3	4 5
Tobacco: yes/no	walking	happy	1	2	3	4 5
____cigs	up/down stairs	stressed	1	2	3	4 5
	sexual activity	tired	1	2	3	4 5
	talking/listening					
Caffeine: yes/no	reading					
____oz	clerical work	HOW MUCH DO YOU FEEL...				
	TV/radio	chest pain	1	2	3	4 5
Alcohol: yes/no	thinking/concentrating	short of breath	1	2	3	4 5
____drinks	waiting					
	other: _____	CIRCLE ONE: alone/with others				

Table 1: Demographic Information Describing CAD Patients with and without Evidence of Ambulatory Myocardial Ischemia.

<u>Demographics</u>	Ischemic CAD (n=9)	Non-Ischemic CAD (n=44)	p-value
Age (years)	69.2 ± 4.0	64.6 ± 7.9	0.09
<u>Gender</u>			
Male	8 (88.9%)	36 (81.8%)	0.52
Female	1 (11.1%)	8 (18.2%)	
<u>Race</u>			
Caucasian	9 (100.0%)	39 (88.6%)	0.57
Non-Caucasian	0 (0.00%)	5 (11.4%)	
Education (years)	15.0 ± 3.0	16.2 ± 2.6	0.23
<u>Clinical History</u>			
Diseased Vessels	1.75 ± 0.9	1.74 ± 0.8	0.98
<u>Previous MI</u>			
Yes	2 (22.2%)	22 (51.2%)	0.11
No	7 (77.8%)	21 (48.8%)	
<u>ETT</u>			
Positive	5 (55.6%)	17 (38.6%)	0.75
Negative	4 (44.4%)	27 (61.4%)	
<u>Previous Angioplasty</u>	5 (55.6%)	19 (43.2%)	0.50
<u>Previous Stent</u>	3 (33.3%)	14 (31.8%)	0.93
<u>NYHA (angina)</u>			
I	7 (77.8%)	40 (90.9%)	0.33
II	2 (22.2%)	3 (6.8%)	
III	0 (0.0%)	1 (2.3%)	
IV	0 (0.0%)	0 (0.0%)	
<u>Medications</u> (prescribed)			
Beta-blockers	6 (66.7%)	27 (61.4%)	0.54
Ca ²⁺ channel blockers	4 (44.4%)	12 (27.3%)	0.31
ACE inhibitors	6 (66.7%)	16 (36.4%)	0.09
Nitroglycerin	2 (22.2%)	16 (36.4%)	0.41
Lipid-lowering	7 (77.8%)	41 (93.2%)	0.33
Aspirin	8 (88.9%)	39 (88.6%)	0.98

Table 2: Information Regarding 18 Recorded Episodes of Ambulatory Myocardial Ischemia in 9 Patients with CAD.

Patient	Episode	Onset Time	Study Day	Duration	ST-segment depression	Heart Rate Prior to the Onset of Ischemia (bpm)			
		(hr:min)				15 min.	10 min.	5 min.	Onset
2	1	7:06	2	43:00	2.0	71	73	74	86
2	2	11:31	2	5:30	1.7	57	62	74	79
8	3	13:26	2	50:00	2.1	61	76	77	100
20	4	11:28	1	3:18	1.4	79	65	86	97
22	5	13:41	2	69:00	1.5	50	50	63	81
23	6	16:52	1	47:00	3.2	64	69	83	99
31	7	14:47	1	38:00	2.8	67	80	92	107
31	8	16:04	1	16:30	2.6	68	107	97	103
31	9	6:55	1	6:48	1.7	79	68	66	81
31	10	8:27	2	2:18	1.1	72	75	81	98
33	11	11:52	1	5:00	1.4	69	71	79	89
33	12	19:51	1	1:15	1.0	62	68	73	75
33	13	21:44	1	19:00	1.3	60	60	70	76
33	14	7:25	1	1:15	1.1	65	58	62	81
36	15	6:02	1	55:45	3.6	78	73	70	104
36	16	19:41	2	15:30	1.0	70	76	94	94
36	17	5:32	2	27:15	2.2	77	76	83	90
48	18	13:24	1	15:25	2.2	86	75	102	112

Table 3: Mean Physical Activity, Blood Pressure, and Heart Rate Levels Measured During 48-Hours of Ambulatory Monitoring.

	N	Physical Activity (counts/minute)	SBP (mm Hg)	DBP (mm Hg)	HR (bpm)
<u>24-hour</u>	49	151.4 ± 81.7	124 ± 11	71 ± 7	66 ± 9
Awake	49	210.1 ± 117.1	126 ± 11	72 ± 8	67 ± 9
Asleep	49	33.8 ± 22.3	113 ± 19	63 ± 8	59 ± 7

Table 4: Range and Mean of Spearman Rank-order Correlations of Patients' Physical Activity Levels with Systolic Blood Pressure, Diastolic Blood Pressure, and Heart Rate.

	N	SBP (mm Hg)	DBP (mm Hg)	HR (bpm)
24-Hour Physical Activity Levels (counts/minute)	49	Correlation Range: $r = -0.13$ to 0.65 Correlation Mean: $r = 0.23 \pm 0.16$	Correlation Range: $r = -0.004$ to 0.60 Correlation Mean: $r = 0.22 \pm 0.14$	Correlation Range: $r = -0.02$ to 0.64 Correlation Mean: $r = 0.35 \pm 0.16$
Awake	49	Correlation Range: $r = -0.18$ to 0.63 Correlation Mean: $r = 0.17 \pm 0.18$	Correlation Range: $r = -0.15$ to 0.59 Correlation Mean: $r = 0.16 \pm 0.16$	Correlation Range: $r = -0.16$ to 0.62 Correlation Mean: $r = 0.29 \pm 0.18$
Asleep	47*	Correlation Range: $r = -0.42$ to 0.79 Correlation Mean: $r = 0.16 \pm 0.33$	Correlation Range: $r = -0.50$ to 0.81 Correlation Mean: $r = 0.10 \pm 0.31$	Correlation Range: $r = -0.25$ to 0.82 Correlation Mean: $r = 0.29 \pm 0.30$

* The physical activity levels of two patients did not vary during sleep, thus limiting the number of patients with activity, blood pressure, and heart rate correlations to 47.

Table 5: Means and Standard Deviations and Statistical Results of Univariate Analyses Comparing CAD Patients with “Low” and ”High” Autonomic Tone on 24-Hour Heart Rate and Blood Pressure Levels and Number of Ischemic Episodes.

	Heart Rate (bpm)	F-value p-value	SBP (mm Hg)	F-value p-value	DBP (mm Hg)	F-value p-value	# Ischemic episodes	F-value p-value
SDNN								
Low (n=26)	70 ± 7	$F_{(1,51)} = 4.67$	125 ± 11	$F_{(1,51)} = 0.17$	71 ± 8	$F_{(1,51)} = 0.38$	0.2 ± 0.7	$F_{(1,51)} = 1.32$
High (n=27)	65 ± 9	$p < 0.05$	123 ± 11	$p = 0.68$	70 ± 7	$p = 0.54$	0.5 ± 1.1	$p = 0.26$
RMSSD								
Low (n=26)	70 ± 8	$F_{(1,51)} = 4.40$	126 ± 12	$F_{(1,51)} = 1.85$	71 ± 9	$F_{(1,51)} = 0.43$	0.2 ± 0.6	$F_{(1,51)} = 2.13$
High (n=27)	65 ± 8	$p < 0.05$	122 ± 10	$p = 0.18$	70 ± 6	$p = 0.52$	0.5 ± 1.1	$p = 0.15$

Table 6: Means and Standard Deviations and Statistical Results of Univariate Analyses Comparing Ischemic and Non-Ischemic CAD Patients on 24-Hour Heart Rate, Blood Pressure, and Autonomic Tone Levels.

	Heart Rate (bpm)	F-value p-value	SBP (mm Hg)	F-value p-value	DBP (mm Hg)	F-value p-value	SDNN (ms)	F-value p-value	RMSSD (ms)	F-value p-value
CAD Patients										
Ischemic (n=9)	63 \pm 8	$F_{(1,51)} = 4.12$	125 \pm 14	$F_{(1,50)} = 0.14$	68 \pm 5	$F_{(1,50)} = 1.78$	172 \pm 25	$F_{(1,51)} = 7.15$	89 \pm 29	$F_{(1,51)} = 0.02$
Non-Ischemic (n=44)	69 \pm 8	$p < 0.05^*$	124 \pm 11	$p = 0.71$	71 \pm 8	$p = 0.19$	141 \pm 34	$p < 0.05^*$	87 \pm 43	$p = 0.90$

* denotes a significant relationship that was opposite to the predicted direction.

Table 7: Means and Standard Deviations and Results of Statistical Analyses Comparing Ischemic and Non-Ischemic CAD Patients on 24-Hour Heart Rate and Blood Pressure Levels and Autonomic Tone During 30-Minute Epochs of “Low” and “High” Physical Activity.

30-minute Period of “Low” Physical Activity												
	HR (bpm)	t-test p-value	SBP (mm Hg)	t-test p-value	DBP (mm Hg)	t-test p-value	HF (ms²)	t-test p-value	LF (ms²)	t-test p-value	LF/HF (ms²)	t-test p-value
CAD Patients*												
Ischemic (n=9)	59 ± 8	t ₍₄₆₎ =2.00	127 ± 19	t ₍₄₆₎ =-1.50	68 ± 9	t ₍₄₆₎ =-0.43	5.1±1.4	t ₍₄₆₎ =0.12	6.1±1.3	t ₍₄₆₎ =-1.05	1.2±0.14	t ₍₄₆₎ =-
Non-Ischemic (n=39)	67 ± 11	p = 0.052	119 ± 13	p = 0.14	66 ± 10	p = 0.67	5.1±1.1	p = 0.90	5.6±1.1	p = 0.30	1.1±0.16	p = 0.

30-minute Period of “High” Physical Activity												
	HR (bpm)	t-test p-value	SBP (mm Hg)	t-test p-value	DBP (mm Hg)	t-test p-value	HF (ms²)	t-test p-value	LF (ms²)	t-test p-value	LF/HF (ms²)	t-test p-value
CAD Patients*												
Ischemic (n=9)	76 ± 19	t ₍₄₆₎ =0.90	138 ± 23	t ₍₃₈₎ =-1.05	73 ± 13	t ₍₃₈₎ =0.47	5.6±2.4	t ₍₄₆₎ =0.18	5.9±2.1	t ₍₄₆₎ =0.58	1.1±0.20	t ₍₄₆₎ =C
Non-Ischemic (n=39)	82 ± 17	p = 0.37	131 ± 14	p = 0.30	75 ± 12	p = 0.64	5.7±1.9	p = 0.86	6.3±2.0	p = 0.57	1.1±0.15	p = 0.

* denotes an attrition in the non-ischemic sample of 5 subjects as a result of HRV data limitations during ECG analyses at Brigham and Womens Hospital, Boston, Massachusetts

Table 8: Mean Physical Activity, HR, and HRV Levels Around the Onset of 18 Episodes of Ambulatory Myocardial Ischemia.

	Time Period Surrounding the Onset of Ambulatory Myocardial Ischemia (minutes)									
	-30	-25	-20	-15	-10	-5	Ischemia	+5	+10	+15
Physical Activity (counts/minute)	117.5±137.2	132.3±173.1	189.4±189.9	296.4±515.1	276.8±210.9	525.3±778.5	588.0±660.3	271.3±352.4	275.7±402.1	304.0±471.
Heart Rate (bpm)	64 ± 8	64 ± 9	66 ± 11	69 ± 9	71 ± 12	79 ± 12	92 ± 11	82 ± 15	75 ± 14	73 ± 13
HRV-HF (ms ²)	4.5 ± 1.2	4.4 ± 1.2	4.6 ± 1.2	5.1 ± 1.6	5.0 ± 2.0	4.7 ± 2.1	4.5 ± 1.9	4.2 ± 1.6	4.9 ± 1.6	4.5 ± 1.3
HRV-LF (ms ²)	5.4 ± 1.0	5.3 ± 0.9	5.3 ± 1.0	5.8 ± 1.1	5.5 ± 1.5	5.6 ± 2.0	5.0 ± 2.1	4.8 ± 1.4	5.5 ± 1.0	5.2 ± 1.1
LF/HF (ms ²)	1.24 ± 0.22	1.23 ± 0.19	1.19 ± 0.18	1.19 ± 0.21	1.18 ± 0.22	1.30 ± 0.36	1.13 ± 0.23	1.20 ± 0.30	1.19 ± 0.26	1.19 ± 0.2

Table 9: Means and Standard Deviations and Results of Contrast Tests Comparing Physical Activity and Heart Rate Levels Measured at the Onset of 18 Episodes of Ambulatory Ischemia with Levels Measured During the 30-Minute Period Preceding the Onset of Ischemia.

	Time Period Preceding the Onset of Ambulatory Myocardial Ischemia (minutes)						
	-30	-25	-20	-15	-10	-5	Ischemia
Physical Activity (counts/minute)	117.5 ± 137.2	132.3 ± 173.1	189.4 ± 189.9	296.4 ± 515.1	276.8 ± 210.9	525.3 ± 778.5	588.0 ± 660.3
Contrast test (vs. onset)	F _(1,17) = 10.90 p < .05	F _(1,17) = 9.93 p < .05	F _(1,17) = 7.76 p < .05	F _(1,17) = 4.92 p < .05	F _(1,17) = 5.59 p < .05	F _(1,17) = 0.65 p = 0.43	
Heart Rate (bpm)	64 ± 8	64 ± 9	66 ± 11	69 ± 9	71 ± 12	79 ± 12	92 ± 11
Contrast test (vs. onset)	F _(1,17) = 122.88 p < .05	F _(1,17) = 118.65 p < .05	F _(1,17) = 177.65 p < .05	F _(1,17) = 91.95 p < .05	F _(1,17) = 73.42 p < .05	F _(1,17) = 40.54 p < .05	

Figure 1: Diurnal Distribution of 18 Recorded Episodes of Ambulatory Myocardial Ischemia

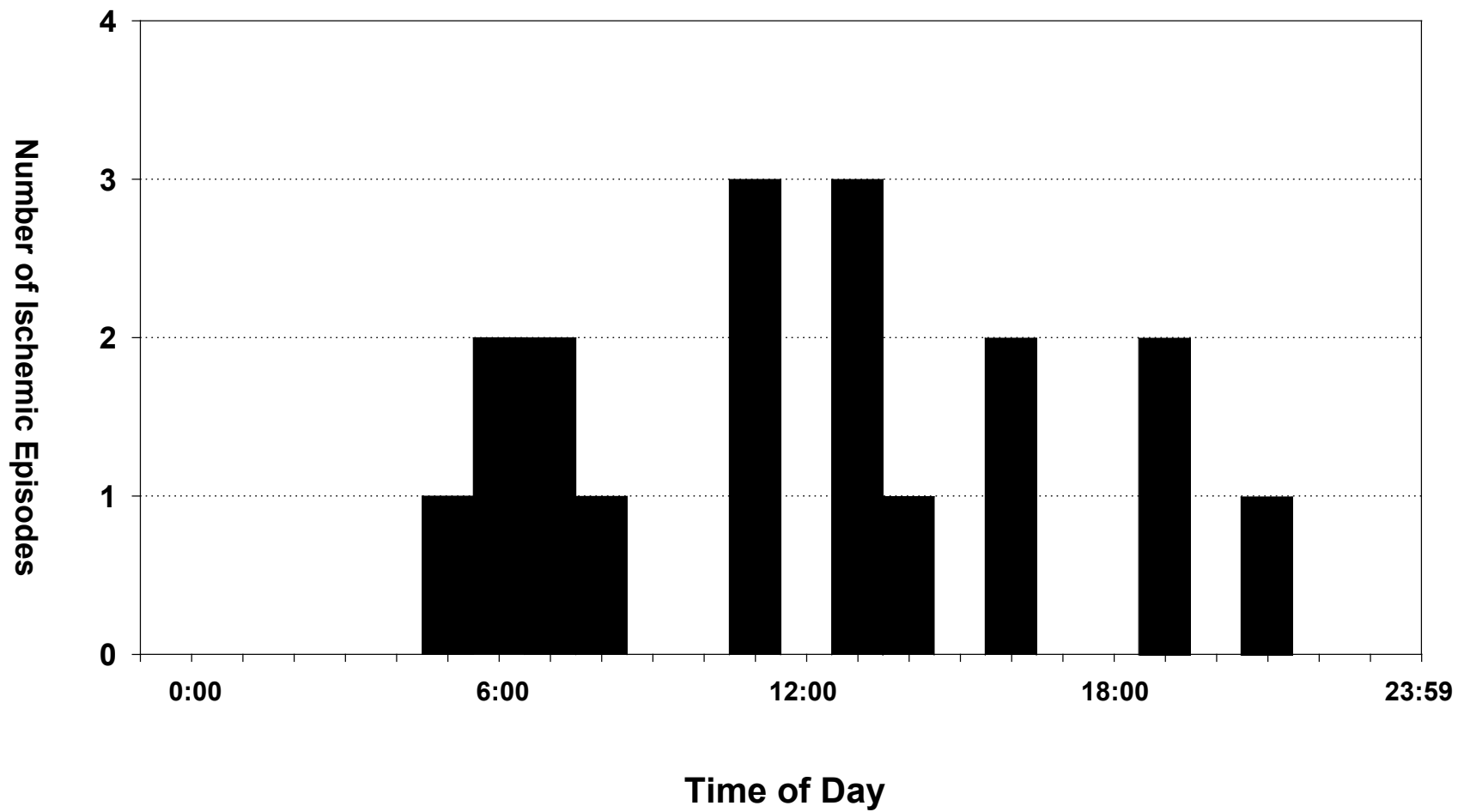


Figure 2: Diurnal Distribution of Mean Ambulatory Physical Activity Levels

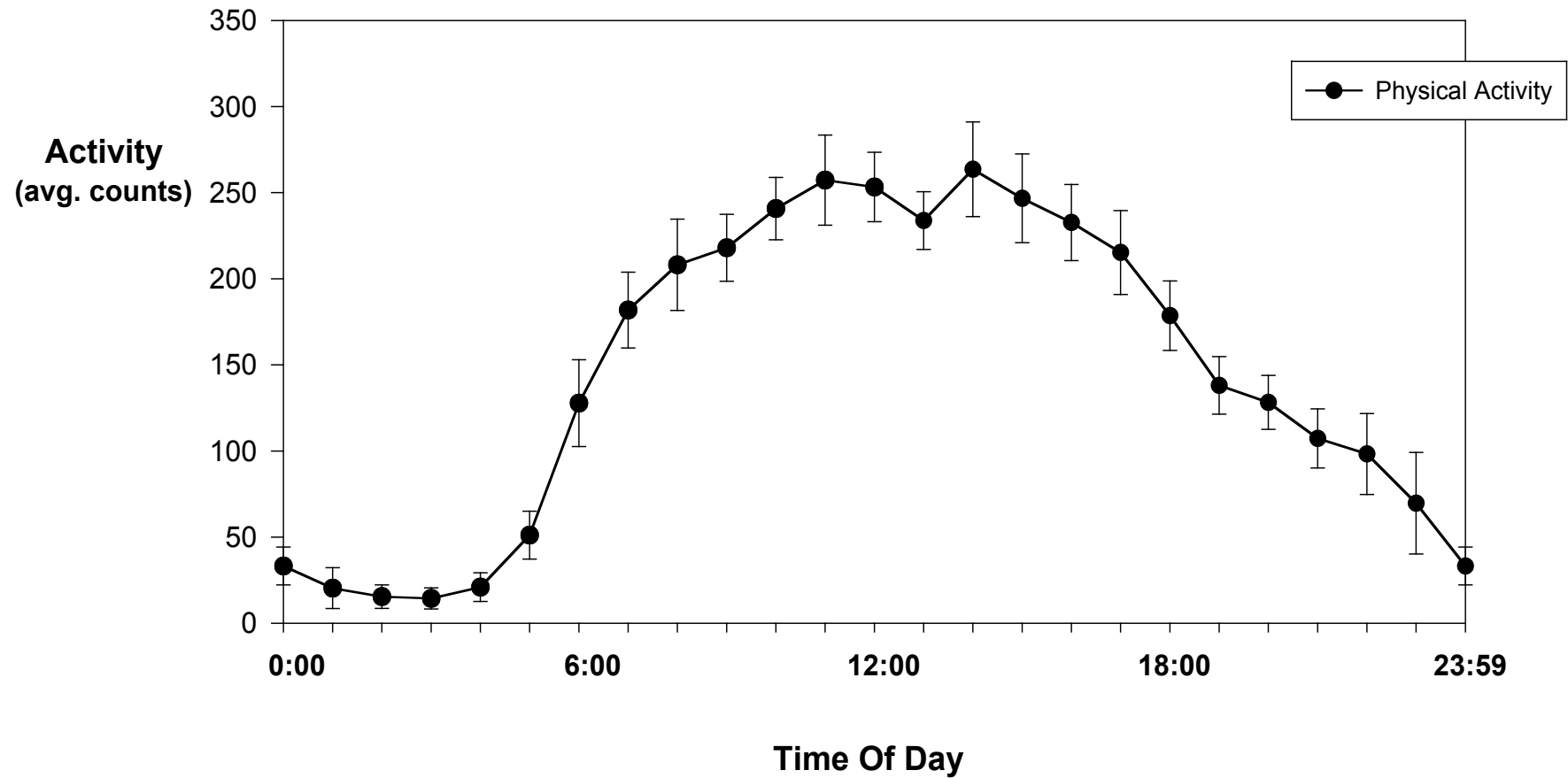


Figure 3: Diurnal Distribution of Mean Hourly SBP and DBP with Respect to Mean Physical Activity Levels

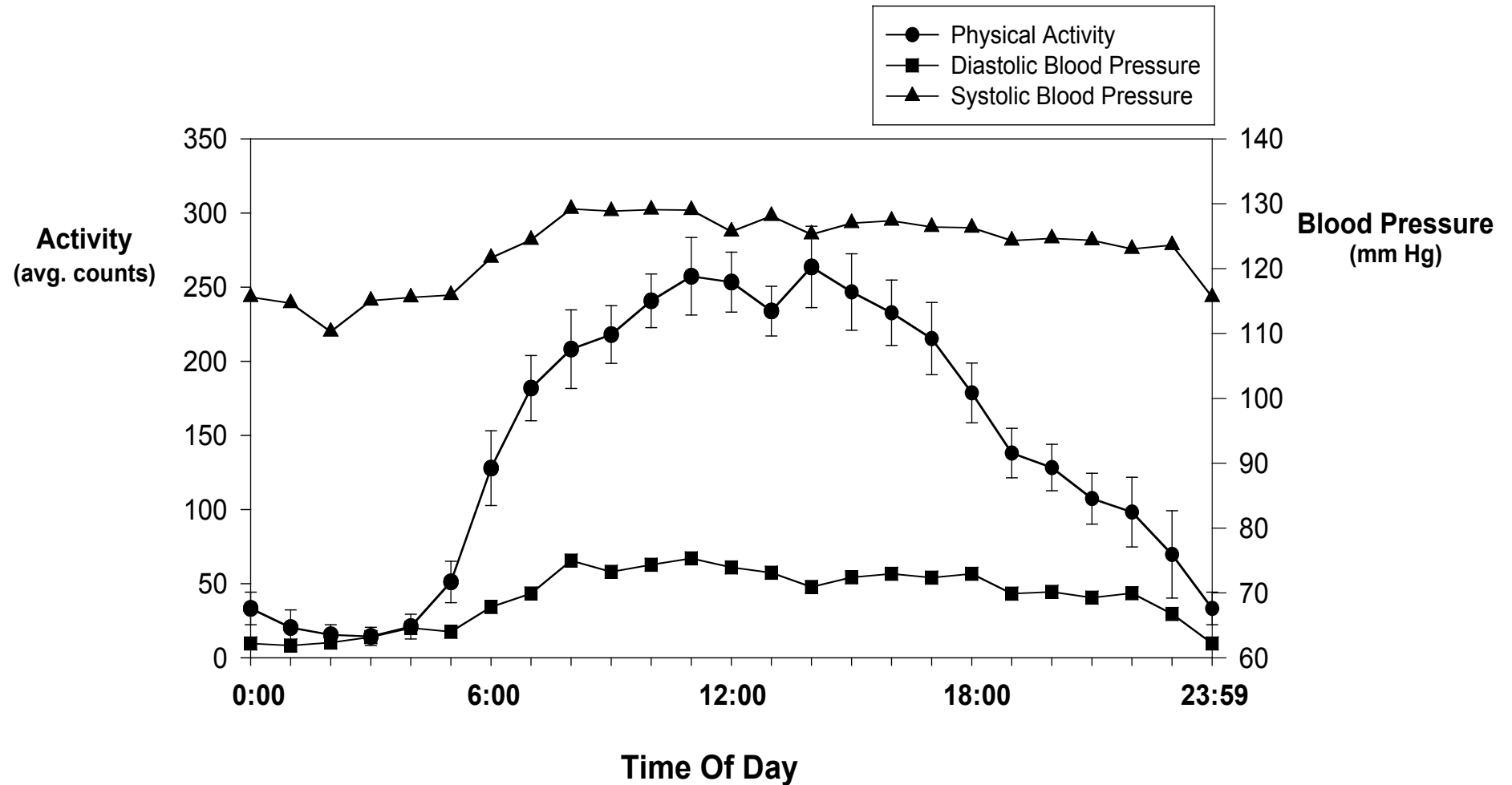


Figure 4: Diurnal Distribution of Mean Heart Rate with Respect to Mean Physical Activity Levels

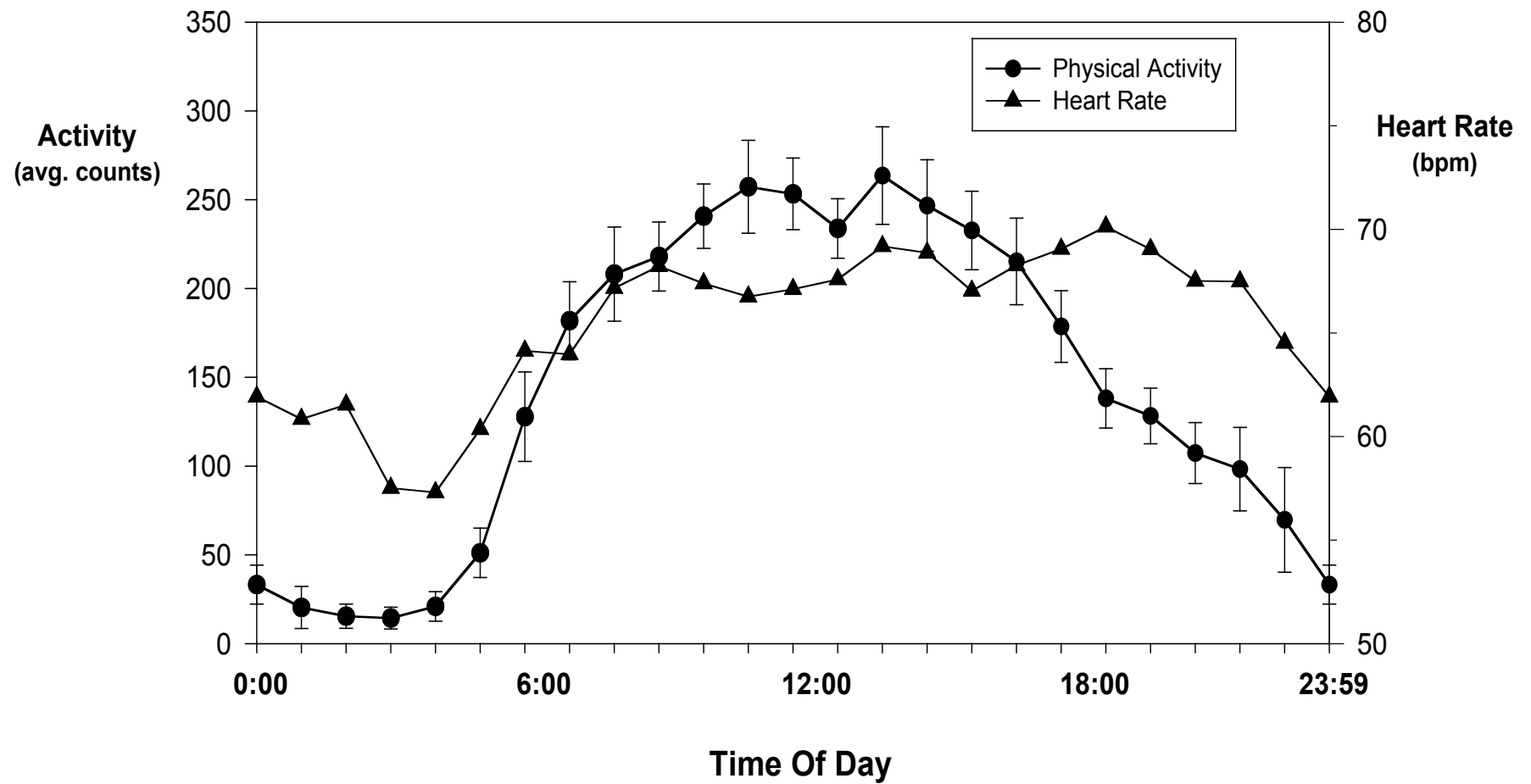


Figure 5: Self-reported Diary Effort Ratings (i.e., 1- 5) for Physical and Mental Activity with Respect to Concurrent Measurements of Mean Ambulatory Physical Activity Levels for the Entire Sample

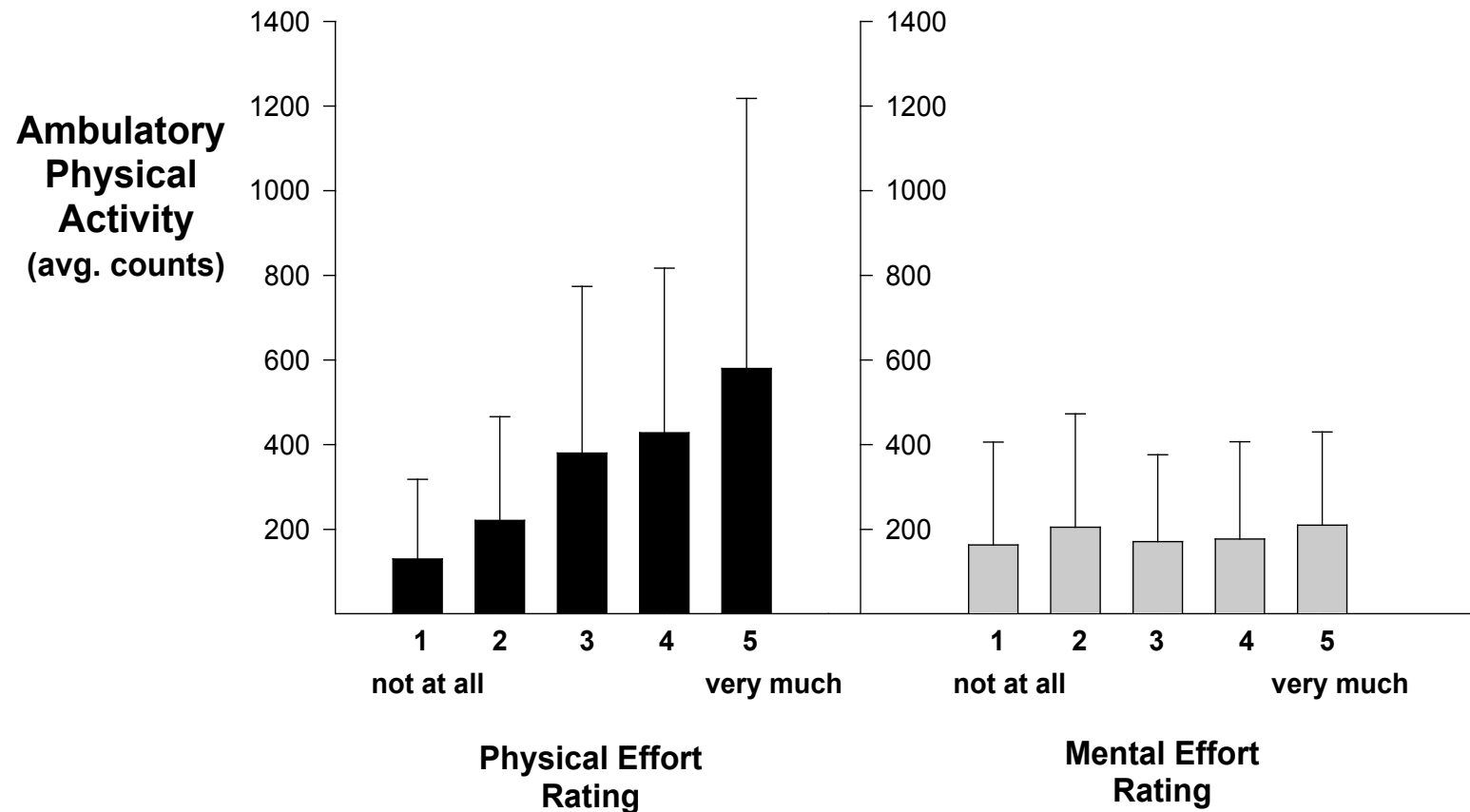
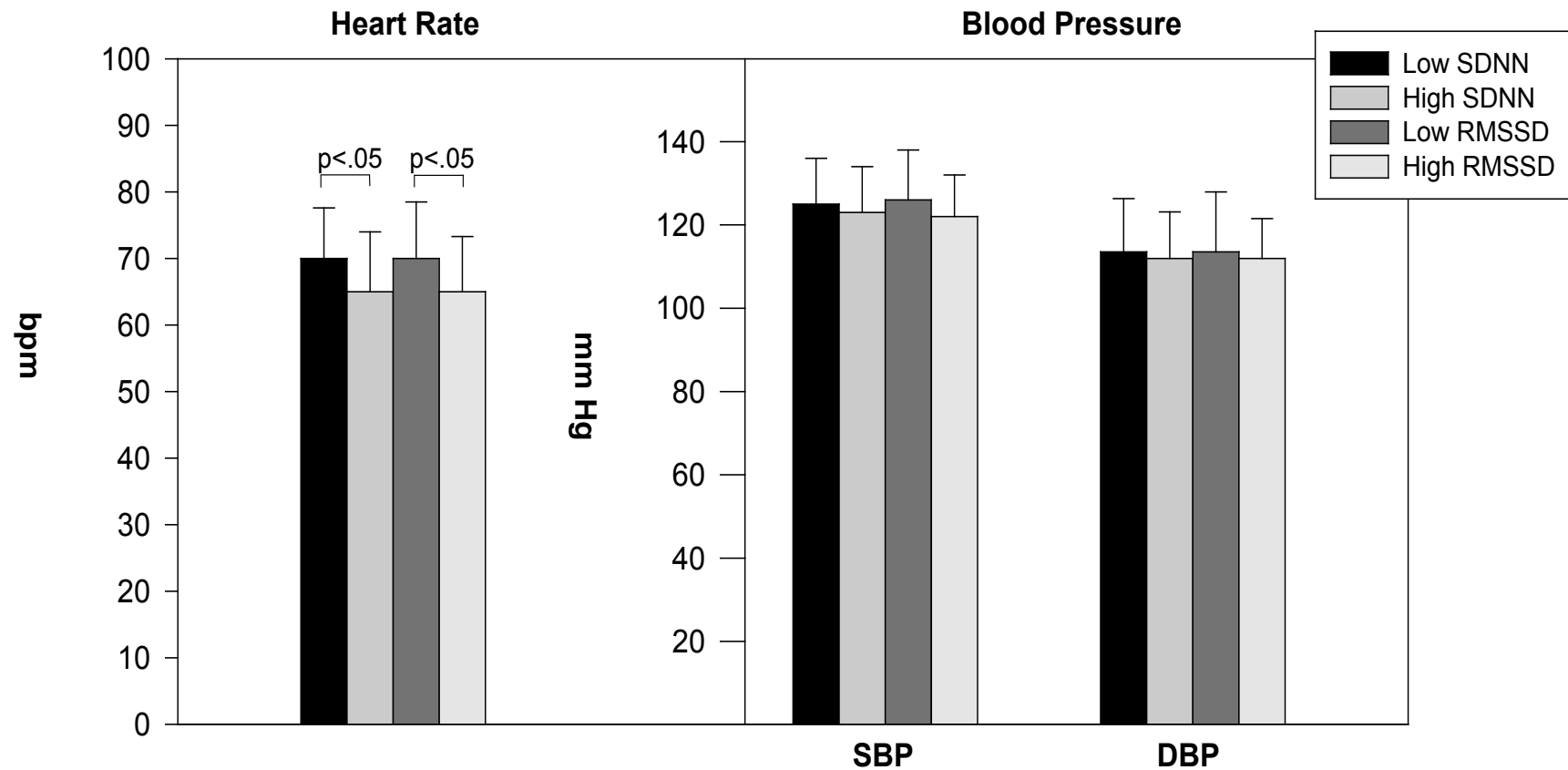
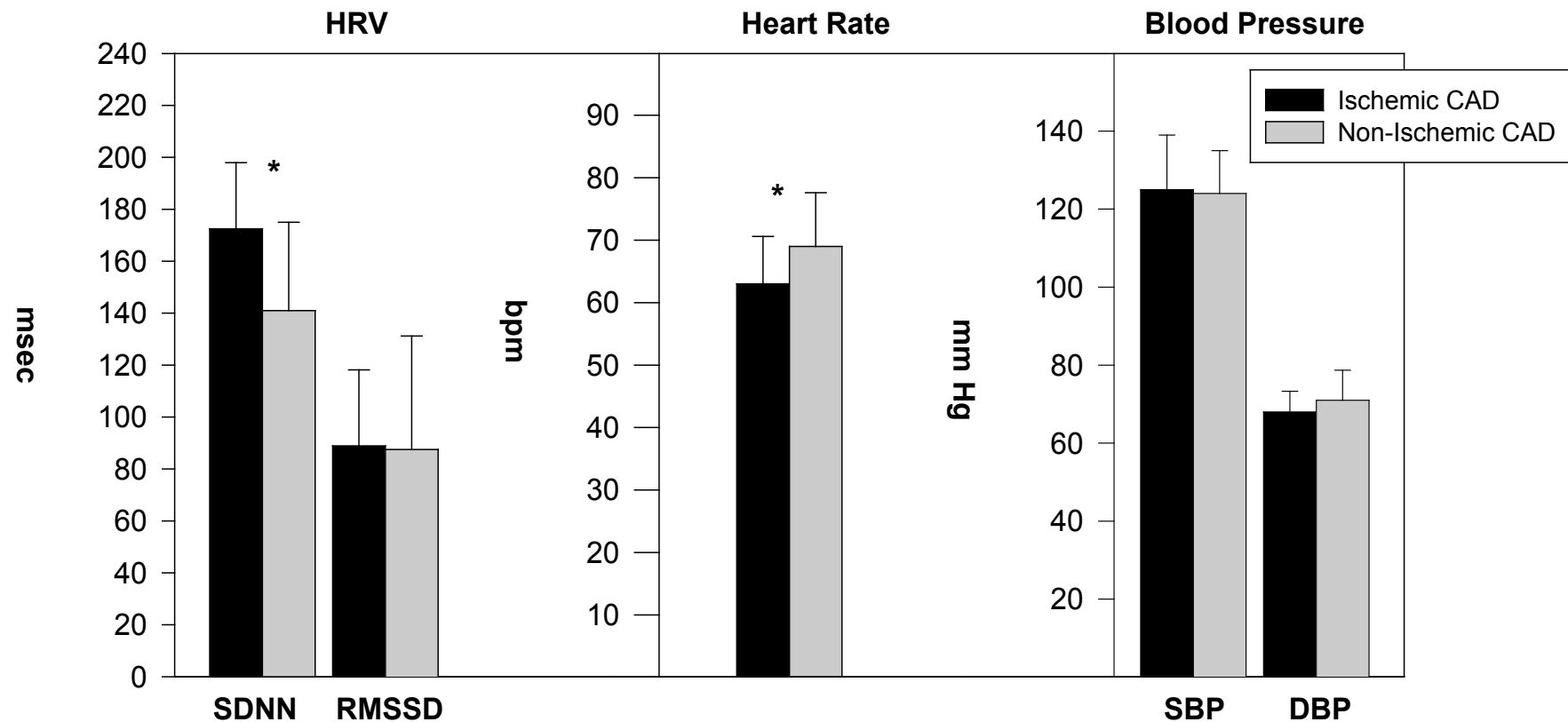


Figure 6: Heart rate and Blood Pressure by 24-hour HRV Indices



SDNN median= 146 ms; range= 76-220 ms
RMSSD median= 73 ms; range= 28-185 ms

Figure 7: 24-hour HRV, Heart Rate, and Blood Pressure for Patients with and without Ischemia



* denotes a significant relationship that was opposite to the predicted direction.

Figure 8: HRV, HR, and BP during 30-minute Non-ischemic Periods of "Low" Ambulatory Physical Activity for Patients with and without Ischemia

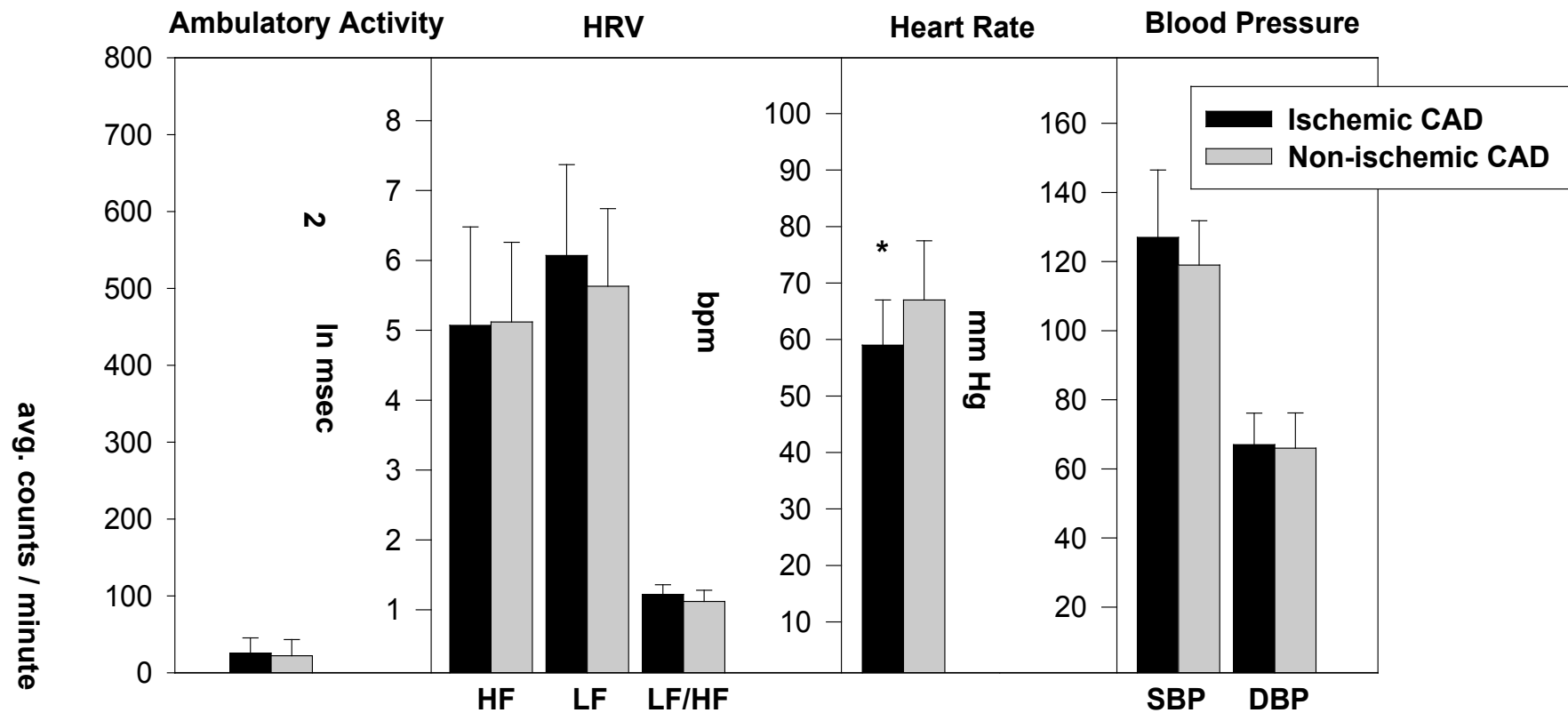


Figure 9: HRV, HR, and BP during 30-minute Non-ischemic Periods of "High" Ambulatory Physical Activity for Patients with and without Ischemia

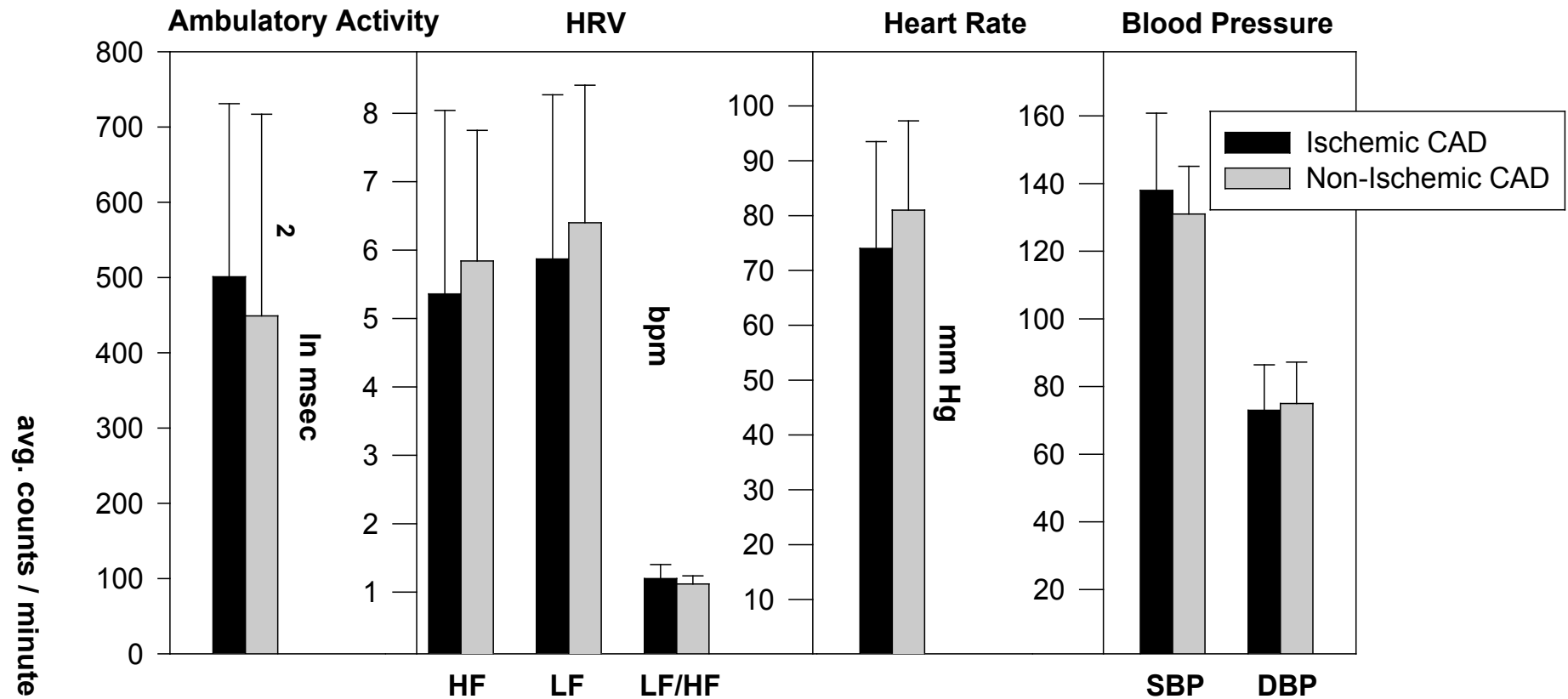
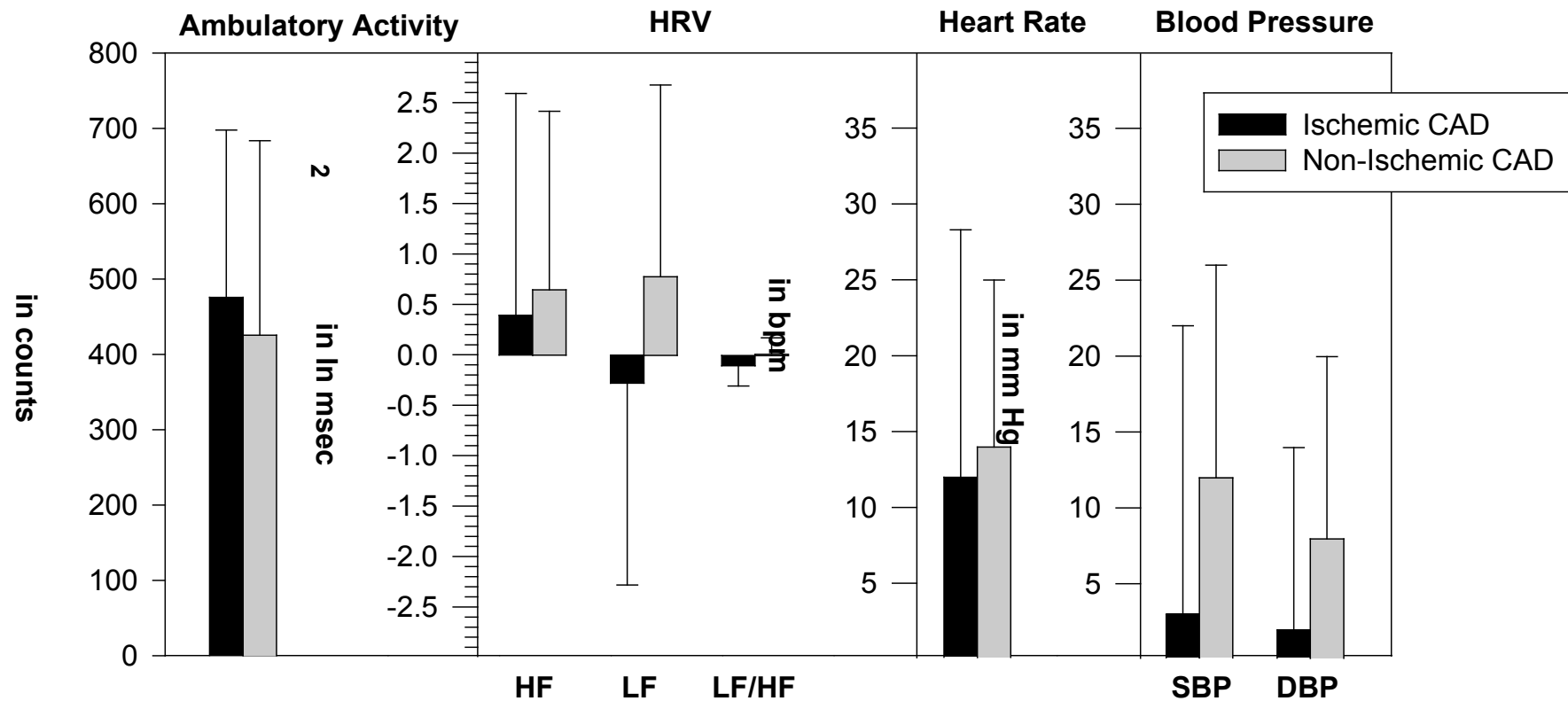
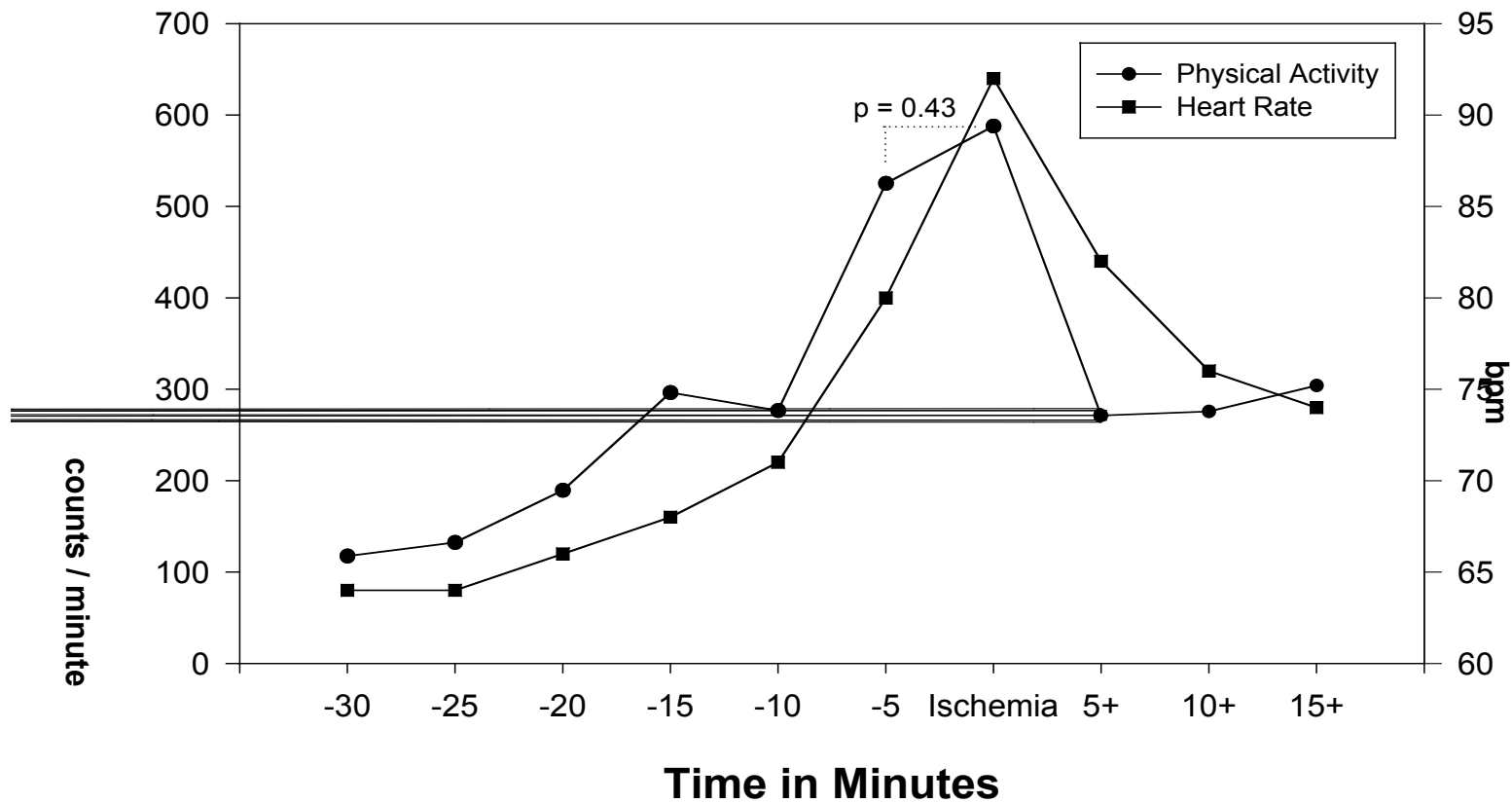


Figure 10: Change in Parameters from Low to High Periods of Non-ischemic Activity for Patients with and without Ischemia



* despite differences in data trends, there were no significant differences observed in change scores.

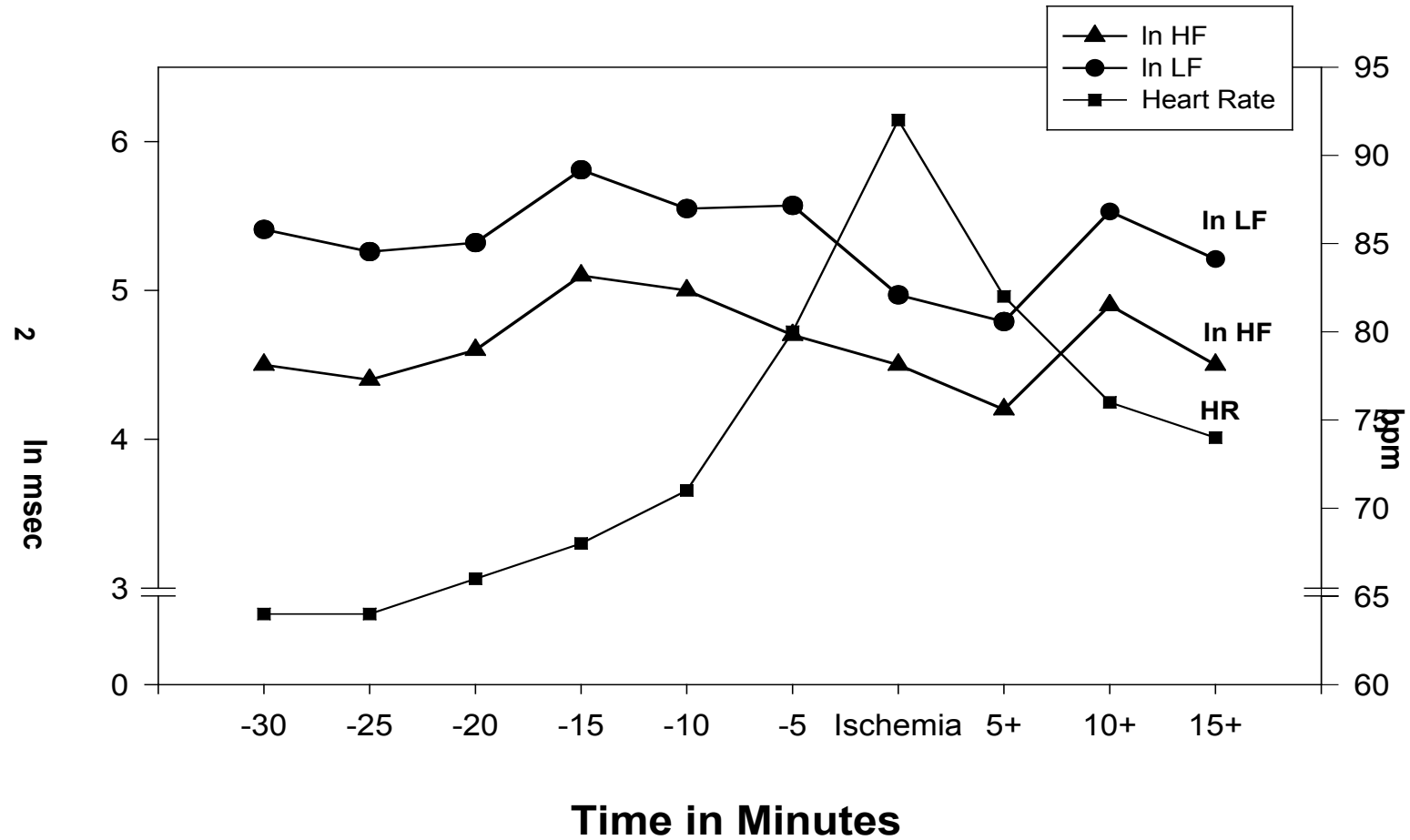
Figure 11: Change in Physical Activity and Heart Rate Around the Onset of 18 Episodes of Myocardial Ischemia



Note 1: Unless otherwise noted, Activity and HR levels at the onset of Ischemia were significantly higher ($p < .05$) than all preceding time point measurements.

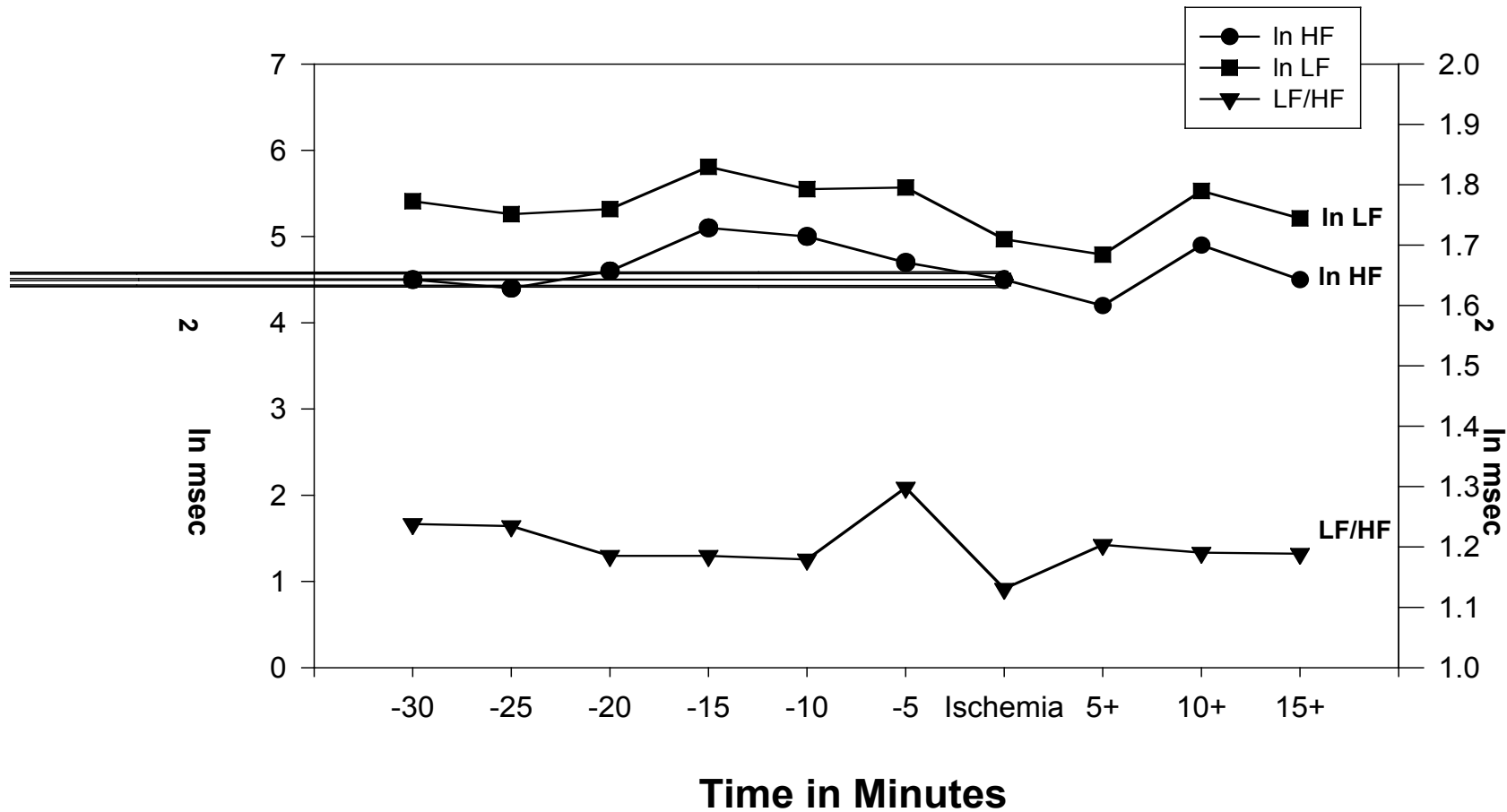
Note 2: Error bars were omitted from this graph for aesthetic purposes.

Figure 12: Change in HF, LF, and Heart Rate Around the Onset of Myocardial Ischemia



Note: Error bars were omitted from this graph for asthetic purposes.

Figure 13: Change in HF, LF, and Sympathovagal Tone (LF/HF) Around the Onset of Myocardial Ischemia



Note: error bars were omitted from this graph for asthetic purposes.

REFERENCES

- Ahonen, A., Harkonen, M., Juntunen, J., Kormano, M. & Penttila, A. (1975). Effects of myocardial infarction on adrenergic nerves of the rat heart muscle, a histochemical study. Acta Physiol Scand, 93, 336-44.
- Airaksinen, K.E., Ikaheimo, M.J., Linnaluoto, M.K., Niemela, M. & Takkunen, J.T. (1987). Impaired vagal heart rate control in coronary artery disease. Br Heart J, 58, 592-7.
- Algra, A., Tijssen, J.G., Roelandt, J.R., Pool, J. & Lubsen, J. (1993). Heart rate variability from 24-hour electrocardiography and the 2-year risk for sudden death. Circulation, 88, 180-5.
- American Heart Association (2003). American Heart Association Internet Website (www.americanheart.org/statistics/04cornry.html). AHA.
- Andreotti, F., Davies, G.J., Hackett, D.R., Khan, M.I., De Bart, A.C., Aber, V.R., Maseri, A. & Kluft, C. (1988). Major circadian fluctuations in fibrinolytic factors and possible relevance to time of onset of myocardial infarction, sudden cardiac death and stroke. Am J Cardiol, 62, 635-7.
- Barry, J., Campbell, S., Yeung, A.C., Raby, K.E. & Selwyn, A.P. (1991). Waking and rising at night as a trigger of myocardial ischemia. Am J Cardiol, 67, 1067-72.

- Barry, J., Selwyn, A.P., Nabel, E.G., Rocco, M.B., Mead, K., Campbell, S. & Rebecca, G. (1988). Frequency of ST-segment depression produced by mental stress in stable angina pectoris from coronary artery disease. Am J Cardiol, 61, 989-93.
- Bernardi, L., Wdowczyk-Szulc, J., Valenti, C., Castoldi, S., Passino, C., Spadacini, G. & Sleight, P. (2000). Effects of controlled breathing, mental activity and mental stress with or without verbalization on heart rate variability. J Am Coll Cardiol, 35, 1462-9.
- Bigger, J.T., Jr., Fleiss, J.L., Rolnitzky, L.M. & Steinman, R.C. (1993). Frequency domain measures of heart period variability to assess risk late after myocardial infarction [published erratum appears in J Am Coll Cardiol 1993 May; 21(6):1537]. J Am Coll Cardiol, 21, 729-36.
- Bigger, J.T., Jr., Fleiss, J.L., Rolnitzky, L.M., Steinman, R.C. & Schneider, W.J. (1991). Time course of recovery of heart period variability after myocardial infarction. J Am Coll Cardiol, 18, 1643-9.
- Bigger, J.T., Jr., Fleiss, J.L., Steinman, R.C., Rolnitzky, L.M., Kleiger, R.E. & Rottman, J.N. (1992). Frequency domain measures of heart period variability and mortality after myocardial infarction. Circulation, 85, 164-71.

Bigger, J.T., Jr., Fleiss, J.L., Steinman, R.C., Rolnitzky, L.M., Schneider, W.J. & Stein, P.K. (1995). RR variability in healthy, middle-aged persons compared with patients with chronic coronary heart disease or recent acute myocardial infarction. Circulation, 91, 1936-43.

Bigger, J.T., Jr., Kleiger, R.E., Fleiss, J.L., Rolnitzky, L.M., Steinman, R.C. & Miller, J.P. (1988). Components of heart rate variability measured during healing of acute myocardial infarction. Am J Cardiol, 61, 208-15.

Blumenthal, J.A., Jiang, W., Waugh, R.A., Frid, D.J., Morris, J.J., Coleman, R.E., Hanson, M., Babyak, M., Thyrum, E.T., Krantz, D.S. & et al. (1995). Mental stress-induced ischemia in the laboratory and ambulatory ischemia during daily life. Association and hemodynamic features. Circulation, 92, 2102-8.

Brezinski, D.A., Tofler, G.H., Muller, J.E., Pohjola-Sintonen, S., Willich, S.N., Schafer, A.I., Czeisler, C.A. & Williams, G.H. (1988). Morning increase in platelet aggregability. Association with assumption of the upright posture. Circulation, 78, 35-40.

Brouwer, J., Portegies, M.J., Haaksma, J., Ven, L.L., Viersma, J.W. & Lie, K.I. (1994). Heart rate variability before, during and after episodes of silent myocardial ischemia. J Am Coll Card Suppl, 320A.

- Burg, M.M., Jain, D., Soufer, R., Kerns, R.D. & Zaret, B.L. (1993). Role of behavioral and psychological factors in mental stress-induced silent left ventricular dysfunction in coronary artery disease. J Am Coll Cardiol, 22, 440-8.
- Burger, A.J. (1999). Circadian patterns of heart rate variability in normals, chronic stable angina and diabetes mellitus. Int J Cardiol, 71, 41-48.
- Burger, A.J. & Kamalesh, M. (1999). Effect of beta-adrenergic blocker therapy on the circadian rhythm of heart rate variability in patients with chronic stable angina pectoris. Am J Cardiol, 83, 596-8, A8.
- Bysritsky, A., Craske, M., Maidenberg, E., Vapnik, T. & Shapiro, D. (1995). Ambulatory monitoring of panic patients during regular activity: A preliminary report. Biol Psych, 38, 648-89.
- Center for Disease Control and Prevention (2000). CDCP Internet Website (www.cdc.gov/nccdphp/cardiov.htm), CDCP.
- Copie, X., Hnatkova, K., Staunton, A., Fei, L., Camm, A.J. & Malik, M. (1996). Predictive power of increased heart rate versus depressed left ventricular ejection fraction and heart rate variability for risk stratification after myocardial infarction. Results of a two-year follow-up study. J Am Coll Cardiol, 27, 270-6.

Dakak, N., Quyyumi, A.A., Eisenhofer, G., Goldstein, D.S. & Cannon, R.O., 3rd (1995).

Sympathetically mediated effects of mental stress on the cardiac microcirculation of patients with coronary artery disease. Am J Cardiol, 76, 125-30.

Deanfield, J.E., Maseri, A., Selwyn, A.P., Ribeiro, P., Chierchia, S., Krikler, S. &

Morgan, M. (1983). Myocardial ischaemia during daily life in patients with stable angina: its relation to symptoms and heart rate changes. Lancet, 2, 753-8.

Deanfield, J.E., Shea, M., Kensett, M., Horlock, P., Wilson, R.A., de Landsheere, C.M. &

Selwyn, A.P. (1984a). Silent myocardial ischaemia due to mental stress. Lancet, 2, 1001-5.

Deanfield, J.E., Shea, M., Ribiero, P., de Landsheere, C.M., Wilson, R.A., Horlock, P. &

Selwyn, A.P. (1984b). Transient ST-segment depression as a marker of myocardial ischemia during daily life. Am J Cardiol, 54, 1195-200.

Deedwania, P.C., Ed. (1997). Circadian Rhythms of Cardiovascular Disorders. Armonk,

Futura Publishing Company, Inc.

Deedwania, P.C. & Nelson, J.R. (1990). Pathophysiology of silent myocardial ischemia

during daily life. Hemodynamic evaluation by simultaneous electrocardiographic and blood pressure monitoring. Circulation, 82, 1296-304.

- Degaute, J.P., van de Borne, P., Linkowski, P. & Van Cauter, E. (1991). Quantitative analysis of the 24-hour blood pressure and heart rate patterns in young men. Hypertension, 18, 199-210.
- Demirel, S., Tukek, T., Akkaya, V., Atilgan, D., Ozcan, M. & Guven, O. (1999). Heart rate variability after coronary artery bypass grafting. Am J Cardiol, 84, 496-7.
- Elashoff, J.D., Dixon, W.J., Crede, K.M. & Fotheringham, N. (1995). nQuery Advisor 3.0.
- Fagraeus, L. & Linnarsson, D. (1976). Autonomic origin of heart rate fluctuations at the onset of muscular exercise. J Appl Physiol, 40, 679-82.
- Farrell, T.G., Bashir, Y., Cripps, T., Malik, M., Poloniecki, J., Bennett, E.D., Ward, D.E. & Camm, A.J. (1991). Risk stratification for arrhythmic events in postinfarction patients based on heart rate variability, ambulatory electrocardiographic variables and the signal-averaged electrocardiogram. J Am Coll Cardiol, 18, 687-97.
- Fujita, M., Tanaka, T., Nakae, I., Tamaki, S., Kihara, Y., Nohara, R. & Sasayama, S. (1998). Importance of alpha 1-sympathetic activity for diurnal change in ischemic threshold in patients with stable angina. Clin Cardiol, 21, 357-61.

- Furlan, R., Guzzetti, S., Crivellaro, W., Dassi, S., Tinelli, M., Baselli, G., Cerutti, S., Lombardi, F., Pagani, M. & Malliani, A. (1990). Continuous 24-hour assessment of the neural regulation of systemic arterial pressure and RR variabilities in ambulant subjects. Circulation, 81, 537-47.
- Gabbay, F.H., Krantz, D.S., Kop, W.J., Hedges, S.M., Klein, J., Gottdiener, J.S. & Rozanski, A. (1996). Triggers of myocardial ischemia during daily life in patients with coronary artery disease: physical and mental activities, anger and smoking. J Am Coll Cardiol, 27, 585-92.
- Gage, J.E., Hess, O.M., Murakami, T., Ritter, M., Grimm, J. & Krayenbuehl, H.P. (1986). Vasoconstriction of stenotic coronary arteries during dynamic exercise in patients with classic angina pectoris: reversibility by nitroglycerin. Circulation, 73, 865-76.
- Goldberg, A.D., Becker, L.C., Bonsall, R., Cohen, J.D., Ketterer, M.W., Kaufman, P.G., Krantz, D.S., Light, K.C., McMahon, R.P., Noreuil, T., Pepine, C.J., Raczynski, J., Stone, P.H., Strother, D., Taylor, H. & Sheps, D.S. (1996). Ischemic, hemodynamic, and neurohormonal responses to mental and exercise stress. Experience from the Psychophysiological Investigations of Myocardial Ischemia Study (PIMI). Circulation, 94, 2402-9.

- Gordon, R.D., Wolfe, L.K., Island, D.P. & Liddle, G.W. (1966). A diurnal rhythm in plasma renin activity in man. J Clin Invest, 45, 1587-92.
- Goseki, Y., Matsubara, T., Takahashi, N., Takeuchi, T. & Ibukiyama, C. (1994). Heart rate variability before the occurrence of silent myocardial ischemia during ambulatory monitoring. Am J Cardiol, 73, 845-9.
- Gottdiener, J.S., Krantz, D.S., Howell, R.H., Hecht, G.M., Klein, J., Falconer, J.J. & Rozanski, A. (1994). Induction of silent myocardial ischemia with mental stress testing: relation to the triggers of ischemia during daily life activities and to ischemic functional severity. J Am Coll Cardiol, 24, 1645-51.
- Gullette, E.C., Blumenthal, J.A., Babyak, M., Jiang, W., Waugh, R.A., Frid, D.J., O'Connor, C.M., Morris, J.J. & Krantz, D.S. (1997). Effects of mental stress on myocardial ischemia during daily life. JAMA, 277, 1521-6.
- Guyton, A.C. & Hall, J.E. (1996). Textbook of Medical Physiology. Philadelphia, W. B. Saunders Company.
- Hartikainen, J., Mustonen, J., Kuikka, J., Vanninen, E. & Kettunen, R. (1997). Cardiac sympathetic denervation in patients with coronary artery disease without previous myocardial infarction. Am J Cardiol, 80, 273-7.

- Hayano, J., Wei, J., Mukai, S., O'Conner, C., Waugh, R., Frid, D., Fujinami, T. & J.A., B. (1994). Autonomic modulation of heart rate before and during transient myocardial ischemia in daily life. J Am Coll Card Suppl, 320A.
- Hedges, S.M., Krantz, D.S., Contrada, R.J. & Rozanski, A. (1990). Development of a diary for use with ambulatory monitoring of mood, activity, and physiological function. J Psychopathol Behav Assess, 12, 203-17.
- Huikuri, H.V. (1995). Heart rate variability in coronary artery disease. J Intern Med, 237, 349-57.
- Huikuri, H.V., Kessler, K.M., Terracall, E., Castellanos, A., Linnaluoto, M.K. & Myerburg, R.J. (1990). Reproducibility and circadian rhythm of heart rate variability in healthy subjects. Am J Cardiol, 65, 391-3.
- Huikuri, H.V., Niemela, M.J., Ojala, S., Rantala, A., Ikaheimo, M.J. & Airaksinen, K.E. (1994). Circadian rhythms of frequency domain measures of heart rate variability in healthy subjects and patients with coronary artery disease. Effects of arousal and upright posture. Circulation, 90, 121-6.
- Kario, K. (1999). Ambulatory physical activity as a determinant of diurnal blood pressure variation. Hypertension, 34 Pt 1, 685-691.

- Kleiger, R.E., Miller, J.P., Bigger, J.T., Jr. & Moss, A.J. (1987). Decreased heart rate variability and its association with increased mortality after acute myocardial infarction. Am J Cardiol, 59, 256-62.
- Kop, W.J. (1997). Acute and chronic psychological risk factors for coronary syndromes: moderating effects of coronary artery disease severity. J Psychosom Res, 43, 167-81.
- Kop, W.J., Gottdiener, J.G., Verdina, R., Howell, R.H., Haddad, A. & Krantz, D.S. (1995). Relation of mental stress and vagal withdrawal to silent ischemia during the activities of daily life. Circulation, 92, I-676.
- Kop, W.J., Krantz, D.S. & Baker, G. (2001). Measures of blood pressure and heart rate variability in behavioral research on cardiovascular disease. Advances in Behavioral Medicine Assessment. Vingerhoets, A., Harwood Academic Publishers GMBH: 393-412.
- Kop, W.J., Verdino, R.J., Gottdiener, J.S., O'Leary, S.T., Bairey Merz, C.N. & Krantz, D.S. (2002). Changes in heart rate and heart rate variability before ambulatory ischemic events. Journal of the American College of Cardiology, 20, 744-5.
- Kral, B.G., Becker, L.C., Blumenthal, R.S., Aversano, T., Fleisher, L.A., Yook, R.M. & Becker, D.M. (1997). Exaggerated reactivity to mental stress is associated with

exercise-induced myocardial ischemia in an asymptomatic high-risk population. Circulation, 96, 4246-53.

Krantz, D.S., Kop, W.J., Gabbay, F.H., Rozanski, A., Barnard, M., Klein, J., Pardo, Y. & Gottdiener, J.S. (1996a). Circadian variation of ambulatory myocardial ischemia. Triggering by daily activities and evidence for an endogenous circadian component. Circulation, 93, 1364-71.

Krantz, D.S., Kop, W.J., Santiago, H.T. & Gottdiener, J.S. (1996b). Mental stress as a trigger of myocardial ischemia and infarction. Cardiol Clin, 14, 271-87.

Kuo, C.D., Chen, G.Y., Lai, S.T., Wang, Y.Y., Shih, C.C. & Wang, J.H. (1999). Sequential changes in heart rate variability after coronary artery bypass grafting. Am J Cardiol, 83, 776-9, A9.

La Veau, P.J., Rozanski, A., Krantz, D.S., Cornell, C.E., Cattanach, L., Zaret, B.L. & Wackers, F.J. (1989). Transient left ventricular dysfunction during provocative mental stress in patients with coronary artery disease. Am Heart J, 118, 1-8.

Lampert, R., Ickovics, J.R., Viscoli, C.J., Horwitz, R.I. & Lee, F.A. (2003). Effects of propranolol on recovery of heart rate variability following acute myocardial infarction and relation to outcome in the Beta-Blocker Heart Attack Trial. American Journal of Cardiology, 91, 137-42.

- Malliani, A., Pagani, M., Lombardi, F. & Cerutti, S. (1991). Cardiovascular neural regulation explored in the frequency domain. Circulation, 84, 482-92.
- Mulcahy, D., Keegan, J., Cunningham, D., Quyyumi, A., Crean, P., Park, A., Wright, C. & Fox, K. (1988). Circadian variation of total ischaemic burden and its alteration with anti-anginal agents. Lancet, 2, 755-9.
- Pagani, M., Lombardi, F., Guzzetti, S., Rimoldi, O., Furlan, R., Pizzinelli, P., Sandrone, G., Malfatto, G., Dell'Orto, S., Piccaluga, E. & et al. (1986). Power spectral analysis of heart rate and arterial pressure variabilities as a marker of sympatho-vagal interaction in man and conscious dog. Circ Res, 59, 178-93.
- Pai, C.H., Hu, W.H. & Ting, C.T. (1995). Does coronary artery disease with stressed myocardial ischemia alter heart rate variability? Chung Hua I Hsueh Tsa Chih (Taipei), 55, 242-7.
- Panza, J.A., Quyyumi, A.A., Diodati, J.G., Callahan, T.S. & Epstein, S.E. (1991). Prediction of the frequency and duration of ambulatory myocardial ischemia in patients with stable coronary artery disease by determination of the ischemic threshold from exercise testing: importance of the exercise protocol. J Am Coll Cardiol, 17, 657-63.

- Pardo, Y., Merz, C.N., Paul-Labrador, M., Velasquez, I., Gottdiener, J.S., Kop, W.J., Krantz, D.S., Rozanski, A., Klein, J. & Peter, T. (1996). Heart rate variability reproducibility and stability using commercially available equipment in coronary artery disease with daily life myocardial ischemia. Am J Cardiol, 78, 866-70.
- Parker, J.D., Testa, M.A., Jimenez, A.H., Tofler, G.H., Muller, J.E., Parker, J.O. & Stone, P.H. (1994). Morning increase in ambulatory ischemia in patients with stable coronary artery disease. Importance of physical activity and increased cardiac demand. Circulation, 89, 604-14.
- Patterson, S.M., Krantz, D.S., Montgomery, L.C., Deuster, P.A., Hedges, S.M. & Nebel, L.E. (1993). Automated physical activity monitoring: validation and comparison with physiological and self-report measures. Psychophysiology, 30, 296-305.
- Pepine, C.J. (1991). Circadian variations in myocardial ischemia. Implications for management. Jama, 265, 386-90.
- Quigley, J.F. (2000). Physical activity as a trigger of ambulatory myocardial ischemia in patients with coronary artery disease: Assessment using automated activity monitors. Department of Medical and Clinical Psychology. Bethesda, Maryland, Uniformed Services University of the Health Sciences.

Quyyumi, A.A. (1990). Circadian rhythms in cardiovascular disease. Am Heart J, 120, 726-33.

Quyyumi, A.A., Panza, J.A., Diodati, J.G., Lakatos, E. & Epstein, S.E. (1992). Circadian variation in ischemic threshold. A mechanism underlying the circadian variation in ischemic events. Circulation, 86, 22-8.

Ralevic, V. & Burnstock, G. (1993). Neural-endothelial interactions in the control of local vascular tone. Austin, Armstrong Printing Co.

Rich, M.W., Saini, J.S., Kleiger, R.E., Carney, R.M., te Velde, A. & Freedland, K.E. (1988). Correlation of heart rate variability with clinical and angiographic variables and late mortality after coronary angiography. Am J Cardiol, 62, 714-7.

Ring, C., Harrison, L.K., Winzer, A., Carroll, D., Drayson, M. & Kendall, M. (2000). Secretory immunoglobulin A and cardiovascular reactions to mental arithmetic, cold pressor, and exercise: effects of alpha-adrenergic blockade. Psychophysiology, 37, 634-643.

Robinson, B.F., Epstein, S.E., Beiser, G.D. & Braunwald, E. (1966). Control of heart rate by the autonomic nervous system. Studies in man on the interrelation between baroreceptor mechanisms and exercise. Circ Res, 19, 400-11.

- Rocco, M.B., Barry, J., Campbell, S., Nabel, E., Cook, E.F., Goldman, L. & Selwyn, A.P. (1987). Circadian variation of transient myocardial ischemia in patients with coronary artery disease. Circulation, 75, 395-400.
- Rosing, D.R., Brakman, P., Redwood, D.R., Goldstein, R.E., Beiser, G.D., Astrup, T. & Epstein, S.E. (1970). Blood fibrinolytic activity in man. Diurnal variation and the response to varying intensities of exercise. Circ Res, 27, 171-84.
- Ross, R. (1993). The pathogenesis of atherosclerosis: a perspective for the 1990s. Nature, 362, 801-9.
- Rozanski, A., Bairey, C.N., Krantz, D.S., Friedman, J., Resser, K.J., Morell, M., Hilton-Chalfen, S., Hestrin, L., Bietendorf, J. & Berman, D.S. (1988). Mental stress and the induction of silent myocardial ischemia in patients with coronary artery disease. N Engl J Med, 318, 1005-12.
- Rozanski, A., Blumenthal, J.A. & Kaplan, J. (1999). Impact of psychological factors on the pathogenesis of cardiovascular disease and implications for therapy. Circulation, 99, 2192-217.
- Rozanski, A., Diamond, G.A., Forrester, J.S., Berman, D.S., Morris, D. & Swan, H.J. (1984). Alternative referent standards for cardiac normality. Implications for diagnostic testing. Ann Intern Med, 101, 164-71.

- Saul, J., Albrecht, P., Berger, R. & Cohen, R. (1988). Analysis of long-term heart rate variability: methods, 1/f scaling and implications. Computers in Cardiology 1987. Washington, DC., IEEE Computer Society Press: 419-22.
- Schang, S.J., Jr. & Pepine, C.J. (1977). Transient asymptomatic S-T segment depression during daily activity. Am J Cardiol, 39, 396-402.
- Schwartz, J.E., Warren, K. & Pickering, T.G. (1994). Mood, location and physical position as predictors of ambulatory blood pressure and heart rate: application of a multi-level random effects model. Ann Behav Med, 16, 210-20.
- Shapiro, D. & Goldstein, I.B. (1998). Wrist actigraph measures of physical activity level and ambulatory blood pressure in healthy elderly persons. Psychophysiology, 35, p305-12.
- Stone, P.H., Krantz, D., McMahon, R., Goldberg, D., Becker, L., Taylor, H., Cohen, J., Freeland, K., Bertolet, B., Kaufman, P. & Sheps, D. (1995). Relationship between mental stress-induced ischemia and ischemia during routine daily activities and during exercise: A PIMI database study. Circulation, 92, I-677.
- Stone, P.H., Krantz, D.S., McMahon, R.P., Goldberg, A.D., Becker, L.C., Chaitman, B.R., Taylor, H.A., Cohen, J.D., Freedland, K.E., Bertolet, B.D., Coughlan, C., Pepine, C.J., Kaufmann, P.G. & Sheps, D.S. (1999). Relationship among mental

stress-induced ischemia and ischemia during daily life and during exercise: the Psychophysiologic Investigations of Myocardial Ischemia (PIMI) study. J Am Coll Cardiol, 33, 1476-84.

Task Force (1996). Heart rate variability: standards of measurement, physiological interpretation and clinical use. Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. Circulation, 93, 1043-65.

Turton, M.B. & Deegan, T. (1974). Circadian variations of plasma catecholamine, cortisol and immunoreactive insulin concentrations in supine subjects. Clin Chim Acta, 55, 389-97.

Vardas, P.E., Kochiadakis, G.E., Manios, E.G., Kanoupakis, E.M., Zouridakis, E.G. & Chlouverakis, G.I. (1996). Spectral analysis of heart rate variability before and during episodes of nocturnal ischaemia in patients with extensive coronary artery disease. Eur Heart J, 17, 388-93.

Vardas, P.E., Skolidis, E.I., Simandirakis, E.N., Parthenakis, F.I., Manios, E.G. & Kochiadakis, G.E. (1994). Autonomic changes before and during nocturnal ischemic episodes in patients with extended coronary heart disease. J Am Coll Card Suppl, 320A.

Webb, S.W., Adgey, A.A. & Pantridge, J.F. (1972). Autonomic disturbance at onset of acute myocardial infarction. Br Med J, 3, 89-92.

Weitzman, E.D., Fukushima, D., Nogeire, C., Roffwarg, H., Gallagher, T.F. & Hellman, L. (1971). Twenty-four hour pattern of the episodic secretion of cortisol in normal subjects. J Clin Endocrinol Metab, 33, 14-22.

Winther, K., Hillegrass, W., Tofler, G.H., Jimenez, A., Brezinski, D.A., Schafer, A.I., Loscalzo, J., Williams, G.H. & Muller, J.E. (1992). Effects on platelet aggregation and fibrolytic activity during upright posture and exercise in healthy men. Am J Cardiol, 70, 1051-1055.

Wolf, M.M., Varigos, G.A., Hunt, D. & Sloman, J.G. (1978). Sinus arrhythmia in acute myocardial infarction. Med J Aust, 2, 52-3.

Yeung, A.C., Vekshtein, V.I., Krantz, D.S., Vita, J.A., Ryan, T.J., Jr., Ganz, P. & Selwyn, A.P. (1991). The effect of atherosclerosis on the vasomotor response of coronary arteries to mental stress. N Engl J Med, 325, 1551-6.

Zeicher, A.M., Drexler, H., Wollschlaeger, H., Saurbier, B. & Just, H. (1989). Coronary vasomotion in response to sympathetic stimulation in humans: importance of the functional integrity of the endothelium. J Am Coll Cardiol, 14, 1181-90.

Zipes, D.P. (1990). Influence of myocardial ischemia and infarction on autonomic innervation of heart. Circulation, 82, 1095-105.